Neurology

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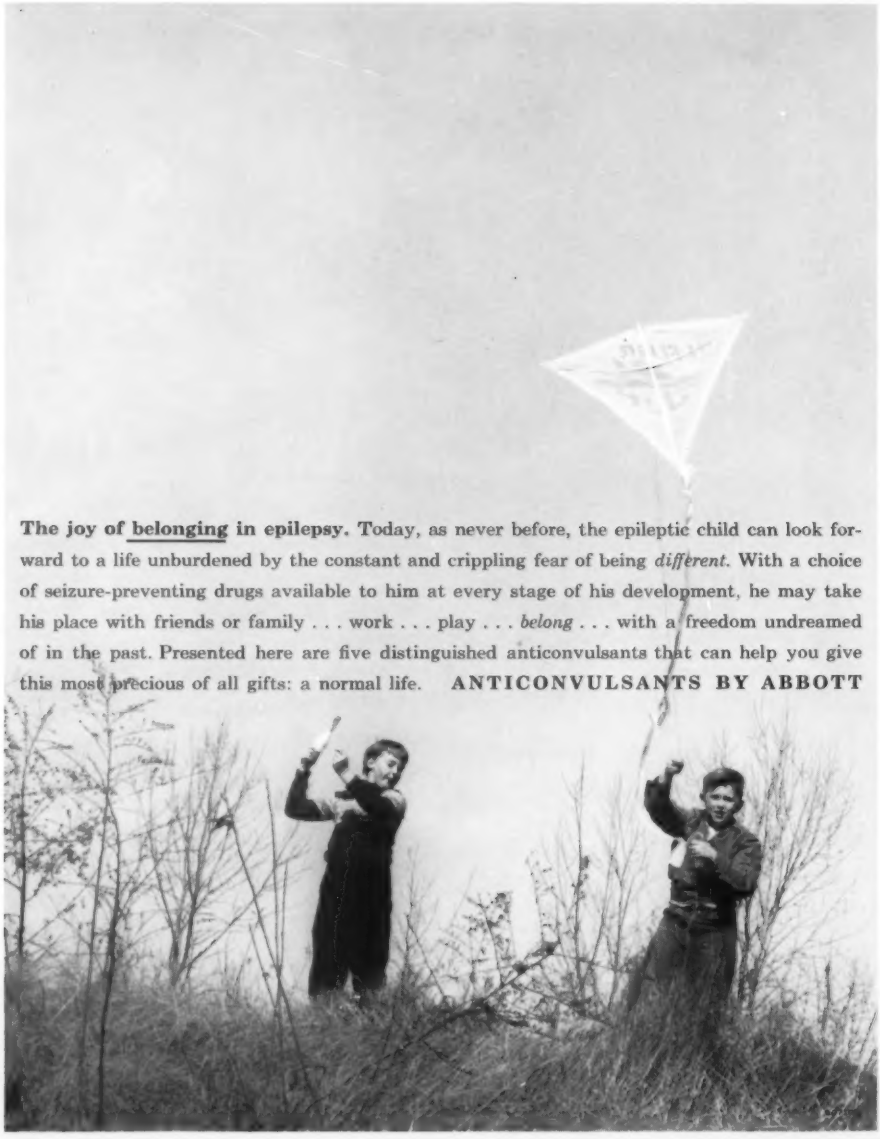

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References: 1. Taylor, I.J.: Clin. Res. Notes 2:1 (Aug.) 1959. 2. Morrow, L.L.: Clin. Res. Notes 2:8 (Aug.) 1959. 3. Darling, H.F.: Dis. Nerv. System 20:167 (April) 1959. 4. Niswander, G.D., and Karacan, I.: Dis. Nerv. System (In Press). 5. Freed, J.E.: Clin. Res. Notes 2:12 (Aug.) 1959. 6. Weiss, I.I.: Clin. Res. Notes 2:12 (Aug.) 1959. 7. Stevenson, L.E.: Clin. Res. Notes 2:10 (Aug.) 1959.

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2. Berris, H.: T. Lancet 74:245 (July) 1954.

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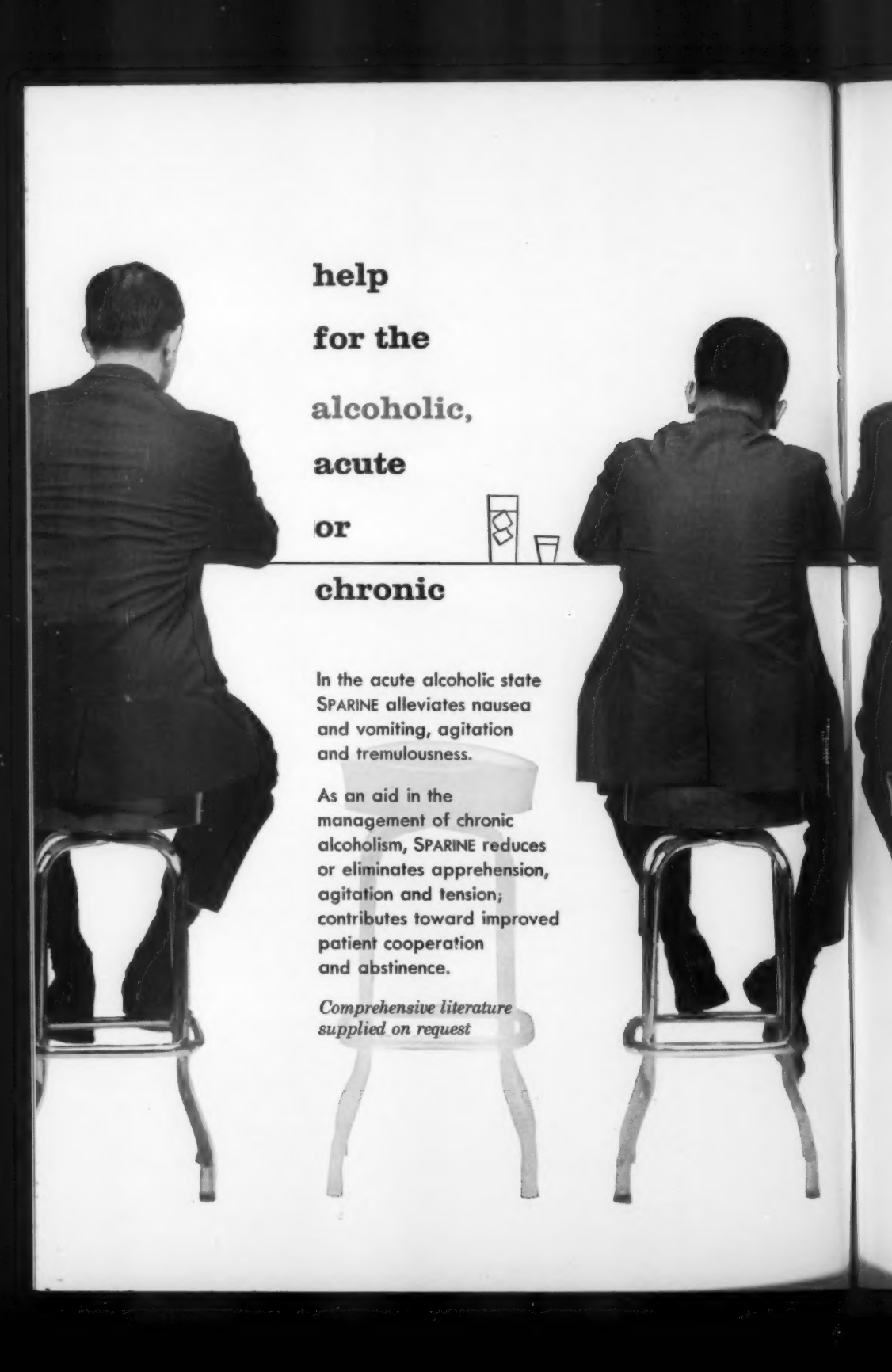
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1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.

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references: 1. Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, *Ann. New York Acad. Sc.* (in press) 1959. 2. Thal, N.: Cumulative Index of Antidepressant Medications, *Dis. Nerv. System* 20:197 (May) 1959. 3. Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, *Am. J. Psychiat.* 116:71 (July) 1959. 4. Arnow, L. E.: Phenelzine: A Therapeutic Agent for Mental Depression, *Clinical Med.*, 6:1573 (Sept.) 1959. 5. Dickel, H. A.; Dixon, H. H.; Shanklin, J. G., and Dixon, H. H., Jr.: Tension Fatigue States and Their Adjunctive Treatment Using Nardil, *Clinical Med.*, 6:1579 (Sept.) 1959.

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Neurology Volume 9 • Number 11

Course and prognosis of acute cerebellar ataxia in children

Stuart Weiss, M.D., and Sidney Carter, M.D.

CERTAIN ataxic syndromes of childhood have been the subject of much interest in recent years, and a number of cases have been reported. The clinical picture of one classic group, described by the term acute cerebellar ataxia, is characterized by the sudden onset, often shortly after a nonspecific infectious disease, of severe gait ataxia with complete recovery within a few months. Case reports by Klingman and Hodges,[1] James,[2] Blaw,[3] Goldwyn[4] (patient 3), Berglund[5] (patients 1 through 4), Cottom[6] (patient 4), and King[7] (patients 3, 6, and 7), described the sequence of events. These authors have emphasized the favorable prognosis implied by this diagnosis. None of these patients, with the exception of 3 of King, were observed for recurrence of neurologic deficit for any extended period beyond recovery from the acute stages of the ataxic syndrome.

Patients 1 and 2 of Goldwyn,[4] 5 and 6 of Berglund,[5] 1, 2, 3, 5, 6, and 7 of Cottom,[6] and Keller's case,[8] examined from one to eight months after the acute illness, and patients 1, 2, 4, 5, 8, and 9 followed by King and associates[7] for six months to ten years cannot be used as case material to demonstrate course and prognosis in the ataxic syndrome of childhood because they had evidence of diffuse cortical or brain stem impairment in the cerebellar deficit in the initial phase of the illness.

Shanks[9] followed 17 patients with cerebellar ataxia. The interval between the acute illness and final examination was not reported; 13 had no neurologic findings on reexamination, 1 had improved over the initial disability, and 3 had deteriorated or were dead. He notes that 9 of the 13 with favorable outcome were asymptomatic within three months of the illness, the other 4 recovering over a three-year period. No information was available concerning his patients with acute ataxia who did not recover. In view of the paucity of information regarding the final outcome of these cases, it seemed desirable to us to reexamine those patients with unequivocal histories of sudden cerebellar involvement to determine if the prognosis is always good and, if not, to what extent does the illness in cases with sequelae differ from the illness in patients who recover.

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Dr. Weiss was a special trainee of the National Institute of Neurological Diseases and Blindness in pediatric neurology.

MATERIAL

Records were reviewed of all patients less than 17 years of age, with diagnoses of ataxia of unknown etiology, encephalitis of the cerebellum, and undiagnosed disease of the central nervous system, who were treated at Columbia–Presbyterian Medical Center in the past twenty years. Criteria for selection of cases for further analysis were: [1] acute onset of neurologic symptoms; [2] signs of cerebellar dysfunction; [3] absence of recent exanthem or exposure to such illnesses; and [4] lack of familial neurologic or skeletal disease. A total of 23 cases were found that satisfied all of these criteria; 18 of the 23 patients, with their parents, were located and were available for reexamination. The original hospital records were carefully reviewed and comprehensive interval histories obtained; all patients had had complete neurologic examinations within the past six months. Although sequelae were present in some cases, none showed evidence of a progressive degenerative disease of the nervous system. These 18 patients were separated into 2 groups according to the time of recovery. The literature to date suggests that the great majority of children who develop acute cerebellar ataxia recover within a six-month period. Group 1 included 10 patients whose neurologic deficit had completely disappeared within six months after onset of symptoms, and group 2 consisted of 8 patients with deficit of more than six months' duration.

ANALYSIS OF MATERIAL

Groups I and II were compared for [1] length of follow-up, [2] age, sex, and race, [3] past history with special emphasis on attainment of developmental milestones, [4] prodromes, [5] initial manifestations of illness, [6] general physical and neurologic findings at time of first hospitalization, [7] laboratory data including special cerebrospinal fluid examinations and blood viral studies, and [8] persistence, severity, and type of neurologic dysfunction during hospitalization and after discharge to the present date.

Length of Follow-up. The interval of time from initial illness to reexamination of the patients ranged from nine months to seventeen years, five years or more having passed since the onset of symptoms in 9 of the 18 children. Group I was followed for an average of six and one-half years, group II for an average of four and one-half years (Fig. 1).

Age, Sex, and Race. At the time of onset of illness, 11 (group I, 5, group II, 6) of the 18 children were between 1 and 2 years old. Of the remaining 7 patients, 2 developed symptoms between the ages of 2 and 3 years, 1 each in their fourth and fifth year, 2 between the ages of 5 and 10, and 1 at the age of 13 (Fig. 2). The age distribution of patients in this study is identical with the experiences of other authors.[1,5,9]

Of the patients, 7 were males and 11, females (Fig. 3). Both sexes were evenly represented among the patients with the prolonged course, group II. Females predominated in group I. Group I of Shanks, with acute onset of cerebellar symptoms and benign prognosis, contained more males than females.

All of the patients in the present series, with the exception of 1 colored child, were of the

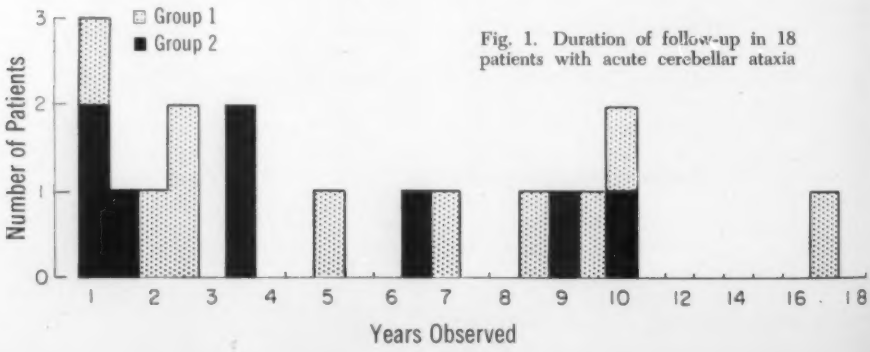

Fig. 1. Duration of follow-up in 18 patients with acute cerebellar ataxia

Caucasian race. Several of the cases of acute ataxia described by Goldwyn[4] and King[7] occurred in Negro children.

The significance of the apparent Caucasian racial predominance and of the more benign prognosis in females in our study is difficult to assess because of the relatively small size of this series and the absence of this type of information in previous case reports.

Past History. Of the 18 children, 12 attained their milestones of psychomotor development at a normal age; 5 children of

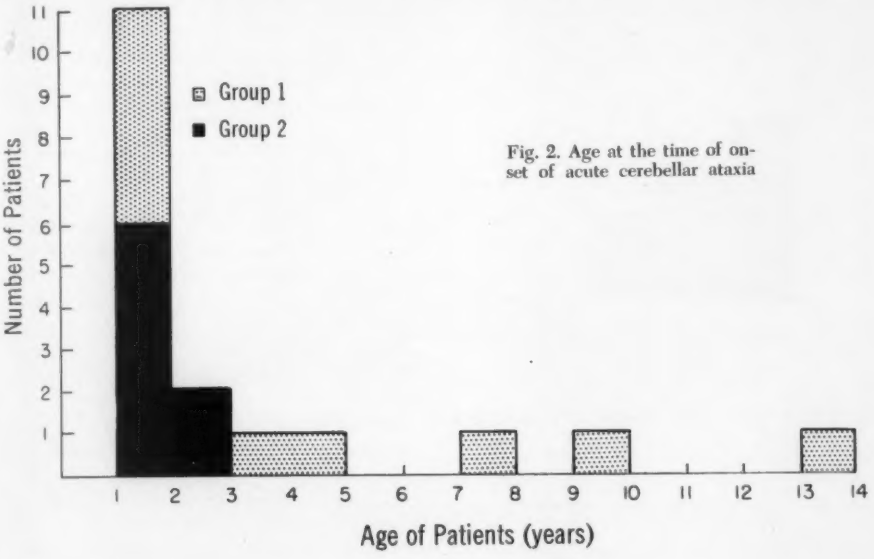

Fig. 2. Age at the time of onset of acute cerebellar ataxia

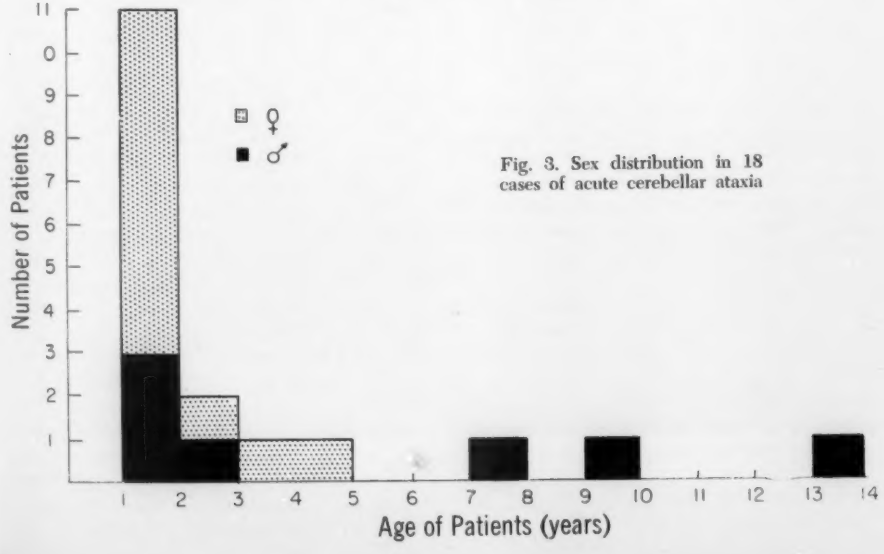

Fig. 3. Sex distribution in 18 cases of acute cerebellar ataxia

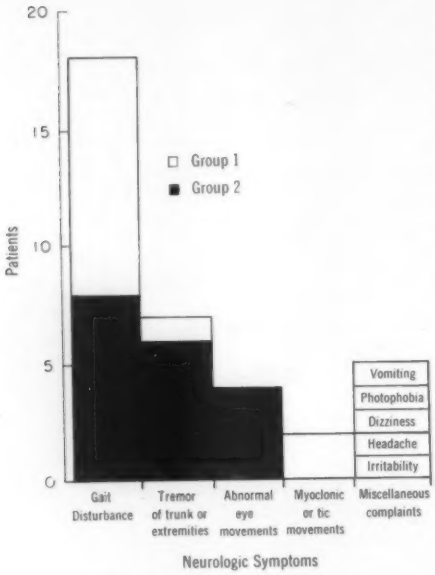

Fig. 4. Initial manifestations in 18 patients with acute cerebellar ataxia

group II were among these, demonstrating a lack of relationship between delay in psychomotor development and poor prognosis of ataxia in this series. The past history of 1 child in group I revealed idiopathic hypoparathyroidism and hepatosplenomegaly as an apparently isolated finding.

In no case did smallpox vaccination or DPT immunization precede the onset of acute cerebellar ataxia; 2 patients, both of group I, received their second injections of Salk vaccine one and three days prior to the onset of the ataxia. There had been no known untoward systemic reaction to the first Salk inoculation in either patient.

Also, 2 children (1 from each group) had received 2 and 3 injections, respectively, of Salk vaccine several months prior to onset of illness. In view of previous assertions of a possible relationship between acute cerebellar ataxia and unusual manifestations of poliomyelitis,[5,11] future reports of all cases of ataxic children who have had the complete series of Salk inoculations will be valuable in determining if such an association is present.

Prodromes. Of the 18 children, 9 had nonspecific, undiagnosed illness one day to three weeks prior to the onset of ataxic symptoms. Of the 9, 5 had fever, 6 had mild upper respiratory symptoms, 2 developed headache and irritability, and 1 experienced symptoms suggestive of gastrointestinal upset; 3 of these 9 (group I) had suffered mild head trauma, without apparent acute or residual damage, one to two and one-half months before they became ataxic. Of the 9 children with prodromal manifestations, 6 were in group I. The other 9 children (5 in group II) gave no history of antecedent illness or trauma before the onset of neurologic deficit.

That there appears to be an association between a type of nonspecific illness and the later onset of acute cerebellar deficit is evident in a significant proportion, 50%, of our cases. This relationship has been noted by other authors. However, from our data, the presence or absence of prodromal illness or history of trauma would seem to have little significance in the prediction of benign or poor prognosis.

Initial Manifestations. The common initial neurologic symptom was rapid deterioration of gait. This varied in degree from minor unsteadiness to complete inability to walk. In many cases, the parents observed that the child had difficulty in maintaining postural tone in a sitting position. This symptom had been present for less than two weeks prior to hospital admission in 13 of the 18 children; 4 of the 5 children whose gait disturbance had been present for longer than two weeks (five weeks to three months), although initially of acute onset and without historic progression, were in group II.

The second most frequent manifestation was spontaneous, often violent tremors. These occurred in 7 cases, involving the head and trunk, and, to a lesser degree, the extremities. The tremor affected axial musculature, usually in static positions, in 5 patients. The other 2 patients had tremor of the extremities on voluntary movement; 6 of the 7 patients were in group II.

The third major symptom was an abnormality of extraocular movement. This was described as a sudden random motion during voluntary eye movement in 2 patients of group II; 2 other children, also in group II, were

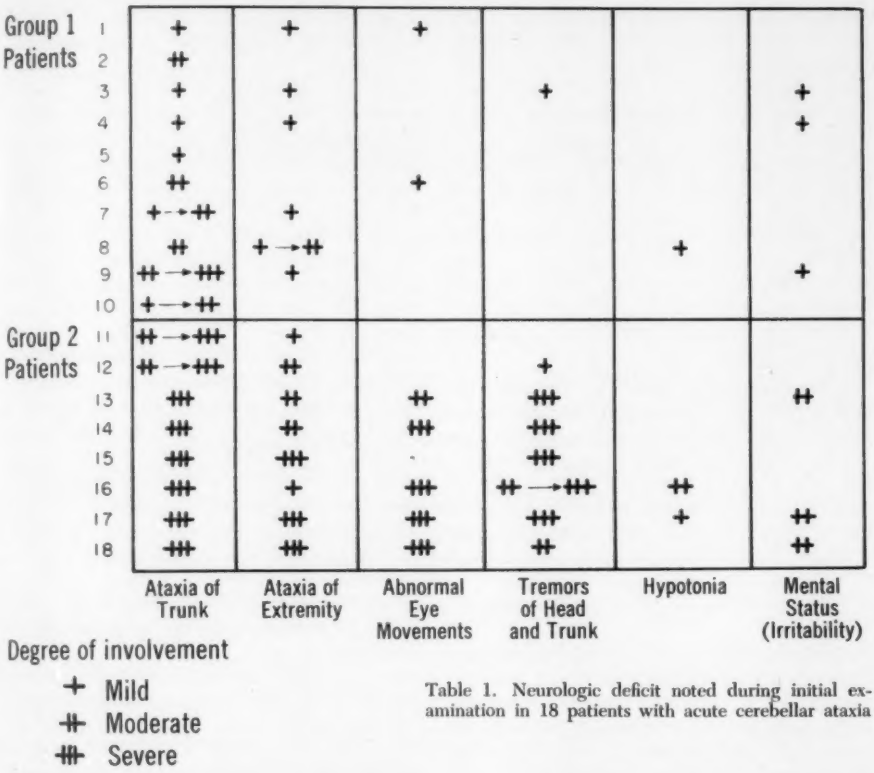

Table 1. Neurologic deficit noted during initial examination in 18 patients with acute cerebellar ataxia

described as having abnormal rhythmic eye movements, nystagmus.

In group I, 2 patients developed myoclonic or "tic-like" movements of the head and arms shortly before admission to the hospital. Although the pathogenesis of such movements is not known and they are not usually considered to be a manifestation of cerebellar dysfunction, their presence in association with gross ataxic gait is of considerable interest.

Miscellaneous symptoms of vomiting, headache, dizziness, photophobia, and irritability were mentioned in the histories of 5 patients, all in group I (Fig. 4).

Physical Findings. All but 3 of the 18 patients were afebrile on admission to hospital; 3 children in group I had temperatures of 100 to 102° F. rectally, which persisted for several days after hospital admission. The child previously diagnosed as having hypoparathyroidism had the only positive physical finding, hepatosplenomegaly, on general examination.

The most noticeable and significant abnormality in the neurologic examination of every patient was moderate to marked truncal ataxia (Table 1). These children staggered and reeled from one side to another, and some were unable to walk or sit without additional support. Of the 8 children in group II, 7 had sudden violent intermittent tremors of the head and body while attempting to maintain balance. A similar tremor of the extraocular muscles was noted in 2 group II children on volitional gaze in any direction. Nystagmus with typical fast and slow components on lateral gaze, distinctly different from the previously described tremor of the eye muscles, was found in five patients, 3 of whom were in group II; 6 of

the 10 children in group I and all of the children in group II exhibited slight to marked degrees of extremity incoordination. Generally, those in the latter group were the more severely incapacitated. A distinct loss of tone was noted in the extremity musculature of 3 patients, 1 in group I and 2 in group II.

In each group, 3 patients were described as "irritable" on admission to the hospital. The significance of this finding without definite change in level of consciousness is difficult to assess in a young child, especially at the time of a major environmental change. Nuchal rigidity, intermittent torticollis, and a Horner's syndrome were single isolated findings in 3 group I children.

Laboratory Data. Initial laboratory evaluation of these children revealed no abnormalities on hemogram, urinalysis, or Mazzini and Mantoux tests. The erythrocyte sedimentation rate was persistently elevated in 2 of the 10 patients in which it was measured. Both of these children were in group I. Examinations of acute and convalescent phase sera for significant antibody titers against eastern and western equine encephalitis, lymphocytic choriomeningitis, and poliomyelitis types I, II, and III were negative in 3 patients. Inoculation from the nose and throat, stool, and cerebrospinal fluid in 1 patient failed to produce any growth on tissue culture. Paul-Bunnell heterophile agglutination titers ranging from 1:4 to 1:128 were found in 8 children but did not change during the period of acute illness and thus were considered nonsignificant. Lead intoxication as a possible etiologic factor was ruled out in 5 cases by radiographic examination of long bones or determination of coproporphyrins in the urine. Routine roentgen examination of the skull was within normal limits in all patients. Electroencephalograms were done in 12 of the 18 children in this series; 4 (1 in group I and 3 in group II) contained excessive amounts of slow activity either diffusely or in both temporal or occipital leads. The other 8 were considered to be within normal limits. Electroencephalograms were made recently on 4 group II children eight months, one year, three years, and six and one-half years after onset of illness. Only the record of the child followed for the shortest period of time was abnormal.

Lumbar punctures were done on 15 of the 18 patients, and 6 of the 15 had multiple cerebrospinal fluid examinations during their hospitalizations. The initial pressure was measured in 11 and found to be normal. A mild pleocytosis of 7 to 25 lymphocytes, which was not present on a later examination, was noted in 5 patients, 3 in group II and 2 in group I. The protein and sugar determinations on all cerebrospinal fluids were normal. This is in contrast to Cottom,[6] who described a protein elevation late in the course of illness. Gamma globulin determinations were made in 4 cases. The only abnormal value, a mild elevation to 17%, was obtained on the cerebrospinal fluid of the child with hypoparathyroidism and increased serum globulin. The colloidal gold test, an indirect assay of globulin, was normal on the cerebrospinal fluid of 2 children, 1 from each group.

Pneumoencephalogram and ventriculogram were done once each during the initial hospitalization with visualization of the entire ventricular system and the basilar cisterns. No abnormalities were found. Because of failure of the cerebellar deficit to improve, pneumoencephalograms were made in 2 patients on subsequent hospitalizations. In 1, six months after onset of illness, a diagnosis of cerebellar atrophy was suggested by dilation of the aqueduct and proximal fourth ventricle; the interpeduncular and pontine cisterns were of normal size and shape, with no evidence of pontine atropy. In the other, the contrast study was interpreted as normal fourteen months after the initial illness.

Course. All the patients in group I showed a persistent gait disturbance from eight days to five months after onset. However, 6 of the 10 were asymptomatic within twenty-one days and 9 within three months after their neurologic deficit appeared; 5 had mild incoordination of voluntary movement of the extremities lasting up to three months, although this mild extremity ataxia disappeared in 3 within one week after onset of illness. Nystagmus persisted in 2 of these children for sixteen and eighteen days, truncal tremor for ten days in 1 patient, and a partial Horner's syndrome for four days in another patient. None were described as having speech impairment or being intellectually retarded. No exacerbations or

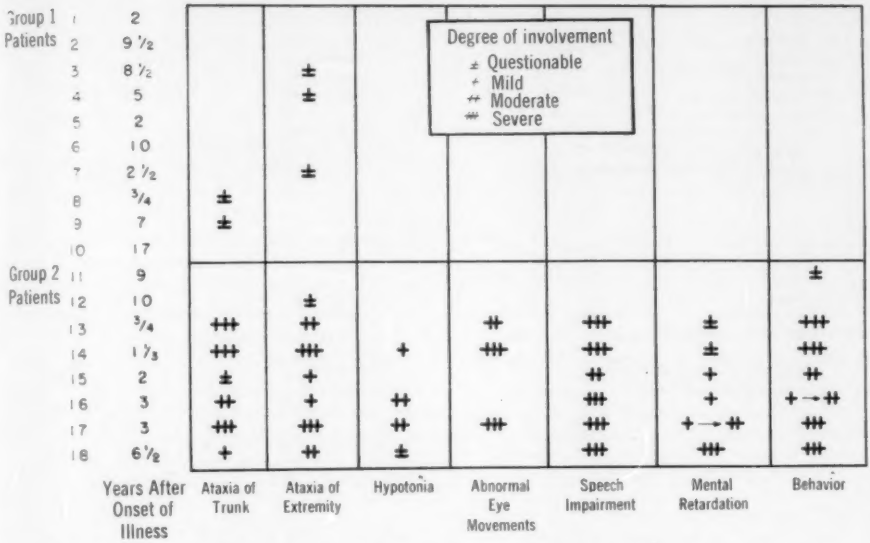

Table 2. Neurologic deficit demonstrated at recent examination of 18 patients with acute cerebellar ataxia

recurrences of neurologic deficit in group I patients were encountered within a period up to seventeen years after the initial illness.

Reexamination of group I children during the present study produced no evidence of major neurologic impairment (Table 2). Minimal difficulty with equilibratory coordination (unsteadiness when standing on 1 foot with the eyes closed) was noted in 2 children, ages 10 and 11 years; 3 children had faint terminal intention tremors on finger to nose testing. Other tests of hand and finger coordination including performance of repetitive movements were normal. Speech was clear and incisive. Brief but thorough evaluation of mental capacity, attitude, and insight produced no evidence of pathology.

In contrast to the quick convalescence and disappearance of neurologic deficit in group I, 6 of the 8 group II patients, followed from nine months to six and one-half years after initial illness, showed persistence of major neurologic findings. The other 2 patients were reported to have unsteady gait for eight months following hospitalization; 1 had truncal tremor and extremity ataxia for five months, then improved. There were no subsequent symptoms, and a neurologic examination ten years after onset of illness revealed only mild intention tremor of upper extremities in this child. The other had what was described in the clinic chart as an increase in symptoms with an upper respiratory infection and fever four months after the original illness. This increase in deficit lasted several weeks. This child, when examined nine years later, was entirely well.

It is quite possible that both of these children belong in group I by history and course of illness, although they were actually placed in group II because their convalescence was prolonged past the six-month interval which separates these groups.

The 6 remaining children in group II, 33% of the entire series, who have been followed for nine months, fourteen months, twenty-two months, three years, three years, and six and one-half years, respectively, have had difficulties suggestive of rather profound neurologic dysfunction over this entire period. All parents commented on diminution of abnormal eye movement as the earliest sign of improvement in their children (Fig. 5D). Present initially in

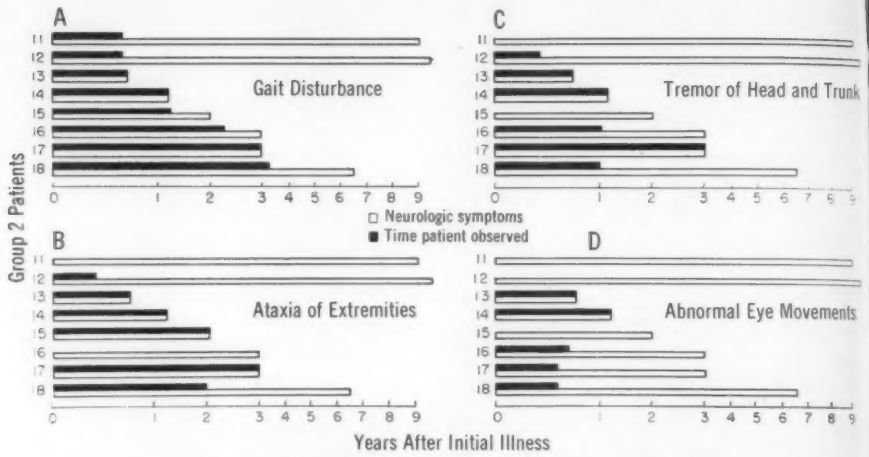

Fig. 5. Persistence of neurologic deficit in 8 patients with acute cerebellar ataxia

5 of the 6 patients, the ataxia of extraocular movement or nystagmus disappeared within eight months in the 3 followed for three to six and one-half years but still persists in the other 2 children, nine and fourteen months after the onset of their illness.

Difficulty with nonequilibratory coordination, especially tremor of the upper extremities on voluntary movement, was severe in 5 of the 6, disappearing completely only in 1 patient two years after onset (Fig. 5B). Moderate improvement was noted in 2 patients followed for two and three years; however, there was little improvement in the 2 patients who were followed for the shortest periods of time, nine and fourteen months. Hypotonia was observed by the parents of 2 children for the entire three years they had been followed. There appeared to be little relationship between those most hypotonic and those with the greatest degree of extremity incoordination. Tremor of axial musculature, initially noted in all, disappeared within one year in the 3 patients followed for periods of two, three, and six and one-half years. There was moderate improvement during the three years another patient was followed but titubation persisted without change in those patients followed for nine and fourteen months (Fig. 5C).

Severe gait disturbance, the earliest symptom and the major neurologic finding during the initial illness, was the most persistent defect and the last to show definite improvement in the 6 group II patients (Fig. 5A); 4 of these children were able to walk without additional support twelve months to three years after onset of symptoms but were still considered awkward by their parents when compared to "normals". Also 2 patients, who had been followed for nine and fourteen months, were unable to sit alone or walk as they had done prior to their illness.

All 6 patients have had speech problems, with poor enunciation, limited vocabulary, or absence of speech to the present date; 3 children, who are now between the ages of 3½ and 4½ years, have small vocabularies of less than 50 words and are just beginning to talk in sentences two to three years after illness. Another patient, age 8, also has a restricted vocabulary and uses only simple sentences six and one-half years after illness. The speech of these 4 children has been showing slow but progressive improvement; 2 patients, both close to 3 years of age, have no understandable speech nine and fourteen months post ataxic syndrome, although they were pronouncing simple words prior to illness. The parents of the 3 older children tend to equate and attribute this speech problem to intellectual im-

pairment which is characterized by difficulty in learning new material, lack of concentration, short attention span, and inability to handle abstract concepts, all manifestations of organic brain damage.

Although none of the 6 patients in group II had a recurrence of neurologic deficit following prolonged or persistent improvement, 2 children, following a course similar to that in a third case described earlier, developed an increase in truncal ataxia two months and five months ofter onset of symptoms. The degree of impairment in gait was not as great as during the initial illness and, in both, occurred in association with low grade fever and upper respiratory infection. Of the 2, 1 has had progressive improvement since, without further relapses during the next six years. The condition of the other patient has not changed in the four months that have passed since the exacerbation of deficit.

Reexamination of the 6 group II children during this study produced objective evidence of dysfunction or impairment in equilibratory and noneequilibratory coordination, speech, and intellectual achievement (Table 2). The degree of deficit in each testing sphere seemed inversely proportional to the length of time which had passed since the patient's illness. Thus, the 2 most recently afflicted children were unable to sit, stand, or walk and did not speak; 3 other children, two to three years after onset of symptoms, were walking awkwardly, exhibited some incoordination of extremities, and had limited vocabularies. The remaining child, six and one-half years after illness, had the least deficit of all on neurologic examination and used a moderate-sized vocabulary during conversation, although it was apparent that her intellectual achievements were on a par with those of a normal 4 year old.

CASE REPORTS

Representative cases typical of both groups in our series are described.

Group I. L.H. was a 16-month-old white female who suffered mild head trauma without sequelae one month prior to hospital admission. Two weeks later, she developed an upper respiratory infection without cough. Three days before hospitalization, her gait became unsteady, causing her to sway from side to side. The past history and psychomotor development were normal.

Physical examination revealed a child with an unsteady, hesitant gait and a tendency to sway in all directions. Nystagmus and extremity ataxia were not present. No abnormalities were noted on any of the laboratory examinations.

Two and one-half months after illness, gait was much improved but still wide based. One month later, all neurologic deficit had disappeared. This child had a negative neurologic examination nine and one-half years after illness. There had been no history of recurrent neurologic deficit.

Group II. M.S. was a 2-year-old white female who developed an upper respiratory infection without fever two weeks before hospitalization. Five days before admission, the child walked unsteadily. One day later, she was noted to have extremity ataxia and irregular eye movements.

Physical examination revealed gross nystagmus on lateral gaze with poor visual fixation. She was unable to walk without support and had ataxia of the extremities on voluntary movement. The child cried with any attempt to change her position.

All laboratory data, including cerebrospinal fluid examination and cultures of throat and spinal fluid for virus, were negative.

The neurologic condition of this patient deteriorated during the first few days in the hospital, with an increase in the truncal ataxia. There was no improvement during the next three weeks of hospitalization, and there has been little during the fourteen months she has been followed since her ataxia began. At the present time, she is able to support her head and sit without aid. She has marked truncal ataxia with truncal tremor and is unable to walk or talk. Ataxia of extraocular movement is present, together with extremity incoordination. Temper tantrums occur with little provocation. A recent pneumoencephalogram was interpreted as being normal.

Group II. S.H. was a 20-month-old white female who developed an upper respiratory infection with mild fever three and one-half weeks before admission to hospital. Several days later, this child developed a sudden gait disturbance. Two weeks before admission, it was noted that she had a severe tremor of the head and was unable to sit unsupported or to focus her eyes.

On physical examination, jerky eye movement with sudden lateral conjugate excursions was noted. Gait was markedly ataxic, wide based, and lurching. Dyssynergia of extremity movement was present. There was no impairment of consciousness.

All laboratory data, including cerebrospinal fluid examination, were within normal limits, except for an electroencephalogram which showed right parietal and temporal slow wave foci. I.Q. was estimated at 95.

At time of discharge from hospital, the child was unable to crawl, walk, or sit and had floppy extremities and gross tremors of the head and arms. During the next three years, she showed progres-

sive improvement and was able to walk and use her upper extremities in a functional manner. I.Q. measured at age 5 was 67. Six and one-half years after the onset of her illness, she still had slight gait disturbance. There was fair coordination of extremities, although fine movement of the hands was grossly impaired. Speech was retarded and very immature. Level of intelligence was estimated at 4 to 5 years.

DISCUSSION

Observation of the course of illness in the few early cases of acute cerebellar ataxia in children reported by Batten[10] and Griffiths[11] and more recently in the patients described by Klingman and Hodges,[1] Blaw,[3] Cottom,[6] Shanks,[9] and King and associates[7] suggested a pattern of rapid recovery even in those whose neurologic deficits had been completely incapacitating. The great majority of these patients had a negative neurologic examination within a few days to six months after the onset of illness. These findings are emphasized in the recent papers, which predict a benign prognosis in patients afflicted with this syndrome. In our series, 10 patients (group I) had a similar course of illness with complete recovery within a six-month period. However, we were most interested in the remaining 8 patients (group II), whose recovery from apparently the same illness was slower and, in some, incomplete. Persistent gait disturbance, truncal tremor, ataxia of extremity movement, abnormal eye movement, and delayed and impaired speech with other signs pointing toward mental retardation were found in 6 of these patients, 33% of the entire series, during the follow-up period of nine months to six and one-half years.

In these 6 children, the neurologic deficit showed progressive improvement that was least in the 2 followed for the shortest period of time. The early age of these children at onset of illness made it difficult to evaluate their mental capacity; however, depression of consciousness, seizures, or stupor was not evident at the time of their hospitalization. The subsequent manifestations of speech and intellectual impairment suggest that there might have been a subtle type of cerebral involvement which could not be detected initially.

The type of persistent neurologic abnormality found in our group II patients parallels Griffith's[11] description of course of illness in cases of acute ataxia, often preceded by infectious disease. He stated that, "although the large brain usually bears the brunt of an encephalitic process, it is perfectly possible for the cerebellum to share or even exhibit the chief symptoms." It is noteworthy that, in Griffith's cases, the diffuseness and severity of cerebral involvement was apparent on initial examination, since he mentions convulsions, stupor, altered consciousness, and motor deficit, along with truncal ataxia, as the major findings in those children, most of whom were more than 6 years old. We would reemphasize that all patients in our series developed ataxia abruptly and were without other evidence of neurologic dysfunction on hospital admission.

Many factors were evaluated in the 2 groups of patients to determine whether the prognosis could be predicted. It was found that age at onset, race, sex, and presence of prodromes were of no significance in the ultimate prognosis of the individual patient. The cerebrospinal fluid examination and other laboratory data obtained at time of initial evaluation likewise proved to be of no value. On the other hand, there was definite correlation between the severity of the initial manifestations of the illness and slow recovery. All patients in group II were markedly incapacitated and had a greater degree of neurologic abnormality on examination at the time of hospital admission.

Much speculation is found in the literature concerning possible etiologies of the syndrome of acute cerebellar ataxia. Demyelinating disease, toxins, allergy, and known and unknown virus infections have been postulated. The prolonged course of 33% of our patients does not support any of these etiologic factors. Demyelinating disease might be considered as a possible etiology in the patients who showed some fluctuation of their ataxia in the early part of their illness. However, the very early age at onset and the lack of any true exacerbations or new neurologic manifestations over the long follow-up period provide suggestive evidence against multiple sclerosis[12,13] or progressive demyelinating disease.

SUMMARY

1] A group of 18 patients with diagnoses of acute cerebellar ataxia was followed for periods of nine months to seventeen years.

2] Of these patients, 10 recovered completely within a six-month period after onset of illness.

3] Neurologic deficit persisted for eight months to six and one-half years in 8 children.

4] The syndrome of acute cerebellar ataxia was not benign in one-third of the patients.

5] The presence of severe cerebellar deficit at onset of illness was correlated with a poor prognosis for recovery.

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Electroencephalographic abnormalties in presenile atrophy

J. M. Swain, M.D.

SINCE THE DIAGNOSIS of cerebral atrophy is based on loss of cerebral substance revealed by roentgenograms made after the injection of air into the ventricular system or on other clinical studies,[1–8] references to electroencephalographic studies in patients with cerebral atrophy usually pertain to a presumably heterogeneous group of disorders.

The following report is a résumé of the case records and electroencephalographic findings in 4 patients with Pick's presenile atrophy and 10 patients with Alzheimer's atrophy in whom histologic verification of the diagnosis is available. Pathologic diagnosis was completed at the neuropathology laboratory of the Langley Porter Neuropsychiatric Institute in San Francisco after examination of the entire brain specimen in 11 patients, and on biopsy material in 1 patient. The remaining 2 patients were diagnosed by the staff pathologist of the Agnews State Hospital.

No case was included in which the histologic evidence was doubtful or in which other cerebral pathology was mentioned. All electroencephalographic tracings were obtained with an Edin machine, using a minimum of 10 electrode placements and a combination of monopolar and bipolar runs. Recordings during sleep and hyperventilation were not available for comparison study in all cases. In interpretation of the records, alpha range was considered to be the frequency range of 8 to 13 cps, theta range 4 to 7 cps, and delta below this. Paroxysmal dysrhythmia was defined as bursts of activity independently or combined with spikes.

Since one of the identifying characteristics of Pick's atrophy is the occurrence of circumscribed, lobar involvement and, conversely, diffuse atrophy is characteristic of Alzheimer's disease, we might reasonably anticipate that the electroencephalographic records would serve to distinguish between the diseases by the absence of focal abnormalities in Alzheimer's disease and the presence of focal abnormalities in Pick's atrophy. Another objective in reviewing the cases described below was to determine whether any identifying trends occurred in the electroencephalographic records which might serve to distinguish the group of presenile atrophies from other progressive degenerative disorders of the brain.

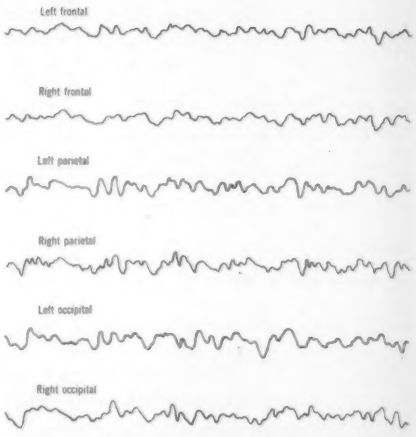

Fig. 1. *(Case 1)* Alzheimer's atrophy. Record shows generalized slowing, with some accentuation in left occipital area.

Case 1. A 66-year-old woman was admitted to the Agnews State Hospital on February 28, 1952, with a deterioration of the intellect and personality which began fifteen to twenty years before. Primarily, symptoms were forgetfulness, inability to concentrate or to carry out simple household chores, and emotional lability.

On examination, the patient was somewhat euphoric and showed marked impairment of mentation and use of language. Tendon reflexes were

Agnews State Hospital, Agnew, Calif.

increased on the left, and the Babinski sign was positive on the left.

A pneumoencephalogram was made in August 1952 which showed marked symmetrical dilation of the ventricles and large collections of air in the subarachnoid spaces about the temporal lobes, enlargement of the basal cisterns, and no apparent increase of air in the sulci over the vertex areas.

An initial electroencephalogram made in March 1952 showed generalized slowing and focal delta activity in the left posterior quadrant (Fig. 1). Subsequently, focal slowing was seen in other areas and paroxysmal bursts became prominent.

Clinical diagnosis was Pick's disease. The patient died on February 22, 1953. The neuropathologist reported Alzheimer's disease with "diffuse degeneration of the layers, particularly the uppermost three, with countless senile plaques and scattered neurofibrillary alterations."

Case 2. A 66-year-old woman was admitted October 19, 1952. Mental deterioration had begun several years previously, and, since 1946, marked symptoms were noticed by the family.

On admission, the patient was incoherent, confused, uncooperative, irrelevant in speech, and unable to attend to any of her personal needs. Physical examination revealed "senile parkinsonism" and evidence of generalized arteriosclerosis. Lumber puncture showed normal pressure, 6 white cells, and 30 mg. protein. Skull films were negative.

An electroencephalogram done October 29, 1952, showed marked generalized slowing of a slightly greater degree posteriorly and higher than average amplitude.

Clinical diagnosis was Alzheimer's disease. The patient died in April 1953. The pathologist reported diffuse atrophy of the cortex which "is noted in all parts of the brain, but somewhat more severe in the lateral than mesial and basal regions . . . the cerebellum was reduced in size."

Case 3. A 60-year-old woman was admitted March 13, 1953. Onset of the patient's illness was ten to fifteen years prior to admission. The first symptoms noted were clumsiness, poor coordination, and progressive intellectual decline. The patient had been hypertensive for two years. A pneumoencephalogram done elsewhere in May 1952 was reported to show diffuse cortical atrophy.

On admission, the patient had unsteady gait, hesitant speech, and aphasia. She had difficulty pronouncing words and was disoriented for time and place. Periods of delusion and hallucination occurred. Lumbar puncture showed normal pressure, 1 cell, and 16 mg. protein.

An electroencephalogram made March 23, 1953, was grossly abnormal—high amplitude 3 to 4 cps activity was superimposed on a basic frequency of 5 to 6 cps. Asymmetry occurred without other focal characteristics.

Clinical diagnosis was Alzheimer's disease. The patient died October 15, 1953. The pathologist reported findings which indicated Alzheimer's atrophy. "The atrophy appears to be uniform throughout the cerebrum and it is moderate in degree."

Case 4. A 62-year-old man was admitted November 20, 1952. Onset of illness had occurred three years earlier. Symptoms were paranoid ideation, anxiety, tremulousness, and inability to complete routine reports required in his job as a laundry truck driver.

On admission, the patient was disoriented, rambling in conversation, confabulatory, and euphoric. No neurologic deficit was otherwise noted. Lumbar puncture revealed normal pressure, 42 white cells, and 37 mg. protein. A pneumoencephalogram made December 30, 1952, showed marked dilation of the ventricular system and increased subarachnoid air, mostly in the basilar cisterns.

An electroencephalogram made December 24, 1952, showed a poorly organized record with only occasional alpha activity. The predominating frequency was in the 5 to 7 cps range with occasional, random low amplitude 2 to 3 cps activity. The record was interpreted as generalized slowing compatible with Alzheimer's disease.

The patient became progressively feeble and incontinent and, in May 1954, had sudden collapse, vomiting, and stupor which suggested vascular accident. Subsequently, he showed some improvement but was only partially ambulatory and spent most of his time in bed sucking and chewing on the bedding. He died December 1, 1955. The pathologist diagnosed Alzheimer's disease. "There is mild to moderate narrowing of the gyri particularly over the frontal poles in the angular and supramarginal gyri and in the anterior half of the superior temporal gyrus. . . . The cerebral cortex shows diffuse degeneration from moderate to severe, the latter particularly in the hippocampus. There are fairly numerous senile plaques throughout the grey matter . . . "

Case 5. A 55-year-old man was admitted November 4, 1953. Air studies made elsewhere were reported to show atrophy. An electroencephalogram made at another hospital was reported as follows: "No definite basic rhythm . . . there was an evident slowing in all leads, especially over the right hemisphere. Imp: Generalized slowing with right sided accentuation."

On admission, the patient was confused. He "wanders about the room and disarranges the bedding, points to the floor, mumbles nonsensical phrases. Unable to recognize simple objects or follow simple directions." Neurologic examination showed the tendon reflexes to be greater on the left. Lumbar puncture showed normal pressure, 0 cells, and 25 mg. of protein.

An electroencephalogram made March 29, 1954, showed marked generalized slowing of greater than average amplitude, mostly in the theta range but with some slower activity present.

The patient developed generalized grand mal seizures and died October 13, 1955. Autopsy

showed "diffuse degenerative changes of the cerebral cortex of uniform severity, characterized by dropping out of neurons, countless senile plaques and neurofibrillary lesions." Diagnosis was Alzheimer's disease.

Case 6. A 61-year-old woman was admitted November 1, 1953. Onset of symptoms occurred four years previously with anxiety, confusion, crying spells, and inability to express herself.

On admission, the patient was agitated, perplexed, aphasic, apractic, and unable to give her name accurately or complete a sentence. She spoke of herself in the third person. She had generally hyperactive reflexes which were greater on the right. Spinal fluid examination was within normal limits. A pneumoencephalogram made November 10, 1953, showed marked increase in subarachnoid air and generalized moderate dilation of the ventricular system compatible with far-advanced cerebral atrophy.

An electroencephalogram showed diffuse and focal slowing which consisted of 2 to 3 cps wave forms from both frontal leads; amplitude was slightly higher than average, and a paucity of alpha rhythm existed.

A seizure was recorded in January 1954. The patient died in May 1955. Her brain revealed the histologic picture of Alzheimer's disease. Atrophy was greater in the prefrontal areas than elsewhere.

Case 7. A 61-year-old woman was admitted October 30, 1955. The patient had come to the state hospital from a rest home and was said to have been confused, disoriented, and afflicted with visual hallucinations of unknown duration. Air studies made elsewhere on May 4, 1954, were reported to demonstrate tremendous dilation of the entire ventricular system without displacement or shift.

On admission, the patient was apractic and confused. She stuttered and did not complete her sentences. She had generalized spasticity and resistance to passive motion which were greater on the right. A grasp reflex was seen on the left and a positive Babinski sign on the right. On 2 occasions, spinal fluid examination was within normal limits and showed no pressure elevation.

An electroencephalogram made December 28, 1955, was grossly abnormal, with generalized slowing and dysrhythmia and focal slowing in the left frontotemporal area. An electroencephalogram on March 19, 1956, showed high amplitude slowing, and spikes coming from all areas without persistent focalization (Fig. 2).

The patient had temperature elevation and left hemiparesis in March 1956. She improved subsequently but died April 12, 1956, with hypostatic congestion and acute interstitial pneumonia. Because of the focal changes which had been noted in the electroencephalogram and in the neurologic examination, a clinical diagnosis of Pick's atrophy seemed possible. Autopsy revealed degenerative changes of Alzheimer's disease.

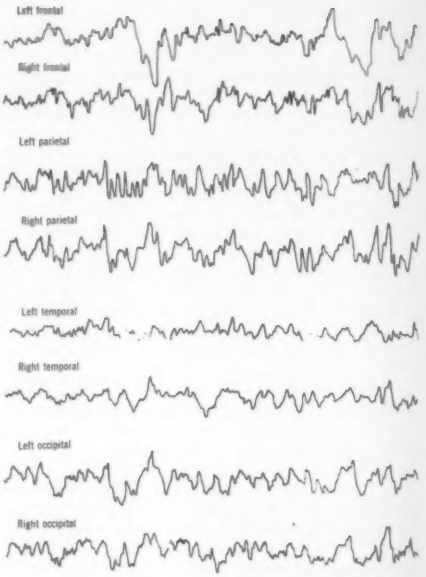

Fig. 2. *(Case 7)* Alzheimer's atrophy. Record shows generalized dysrhythmia of increased amplitude.

Case 8. A 58-year-old woman was admitted January 11, 1953. She was confused, depressed, and agitated. Her sister had been hospitalized for mental illness during middle age but had apparently recovered. Another sister had committed suicide. About one year before admission, the patient had become depressed and received 6 electroshock treatments which seemed to increase her symptoms. She became gradually more confused, was subject to outbursts of anger, and was unable to carry out simple household duties.

On admission, the patient appeared alert superficially but was actually disoriented and had an expressive aphasia. Examination was not otherwise unusual.

An electroencephalogram made February 24, 1953, showed a 10 cycle rhythm, but the predominant frequency was 5 to 6 cps. Activity occasionally became paroxysmal. Some focal 3 cps slow activity of relatively high amplitude occurred from both sides anteriorly (Fig. 3).

A pneumoencephalogram made in March 1953 showed normal-sized ventricles but generalized increase in the subarachnoid air. The patient's husband, who was a physician, was anxious that a lobotomy procedure be done because of the depressive symptomatology. At his urging, despite the diagnosis of degenerative brain disease, a left unilateral prefrontal leukotomy was done. Tissue

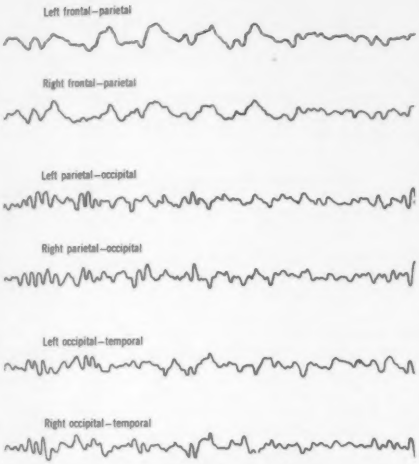

Fig. 3. *(Case 8)* Alzheimer's atrophy. Record shows generalized slowing with focal accentuation in the anterior quadrants bilaterally.

was removed at that time for histologic examination. The pathologist's report indicated changes of Alzheimer's cortical degeneration. The patient was relieved of much of her depression but became hostile and negativistic, deteriorated increasingly, and developed grand mal seizures. She is still living.

Case 9. A 62-year-old woman was admitted March 15, 1956, and died February 18, 1957. The mother and a paternal aunt were said to have had senile psychosis. Confusion and impairment of judgment and memory became evident sixteen years prior to the patient's admission.

Physical examination revealed generalized arteriosclerosis. No neurologic abnormalities were described. Routine skull films and spinal fluid examination were within normal limits.

An electroencephalogram made January 29, 1957, showed almost no frequencies in the alpha range, rambling disorganized slower frequencies throughout, and fast and slow spikes from all areas.

Autopsy findings included bronchopneumonia, hypostatic congestion of the lungs, and Alzheimer's atrophy of the brain.

Case 10. A 60-year-old woman was admitted July 1, 1953. She had been forgetful for eight years and had been treated with insulin shock in a private institution in New York City six years before admission. The patient had been unable to do simple tasks—such as dressing herself—for at least three years.

On admission, she was confused and was not able to verbalize spontaneously. Occasional phrases were blurted out in an attempt to reply. She was unable to follow simple directions or mimic movements, and she was euphoric. A fine tremor occurred in her hands and perioral region. A pneumoencephalogram made October 7, 1953, showed increased subarachnoid air, especially over the frontal areas.

An electroencephalogram made September 25, 1953, showed amplitude increase and slowing from all areas. A few bursts of generalized spiking and occasional isolated spikes were seen.

The patient developed seizures and became bedfast. She died April 28, 1957, of bronchopneumonia and hemorrhagic infarction of the middle and lower lobes on the right lung. The brain showed changes of Alzheimer's disease. "The cortex shows focal areas of atrophy that are, however, of moderate degree and not sharply outlined. These areas are observed in the inferior parietal lobule, diffusely in the three temporal gyri, and fusiform gyrus, and throughout the frontal lobe anterior to one precentral gyrus. . . . There are countless senile plaques and neurofibrillary lesions throughout the cerebral cortex."

Case 11. A 62-year-old woman was admitted in August 1949. She had been employed as a stenographer and had had a mental breakdown in 1919 and again in 1946. She was hospitalized in 1946 and received electroshock therapy. Recovery was never satisfactory. The patient was unable to keep a position and became compulsive and preoccupied with minutiae, although she made many errors. She was irresponsible, confused, and restless and threatened suicide.

On admission, she was tearful, depressed, evasive, and uncommunicative. General physical and neurologic examination was unremarkable. A pneumoencephalogram done December 31, 1952, was reported to show "bilateral but unequal dilatation of the lateral ventricles, the left being considerably larger than the right. There is no evidence of shift in the mid-plane. There is moderate dilatation of the spaces about the isle of Reil. The changes suggest considerable cerebral atrophy."

An electroencephalogram done December 31, 1952, preceding the air studies, was reported to show normal amplitude 8 to 9 cycle rhythm and was interpreted as probably normal (Fig. 4). Review of this record now suggests an increase in the amount of theta rhythms without focal changes. The slowing noted was far less conspicuous than that present in the records of the preceding cases.

Postmortem examination of the brain showed "cortical atrophy in symmetrical areas of the frontal lobes, severely involving all of the gyri on the lateral aspects from the tips up to the pre-central sulci. On the base only moderate involvement of the orbital and rectus gyri. Vague areas of mild atrophy noted in the inferior parietal region on the right side." The pathologist's diagnosis was Pick's disease.

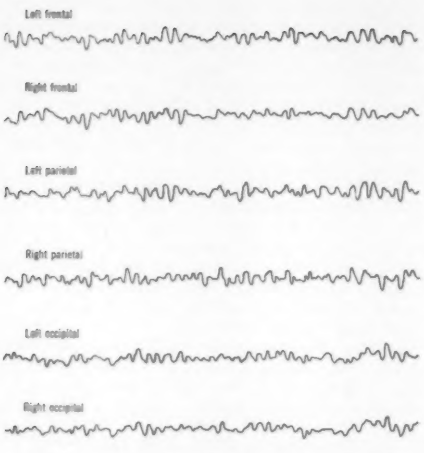

Fig. 4. *(Case 11)* Pick's atrophy. Record shows generalized slowing of relatively mild degree.

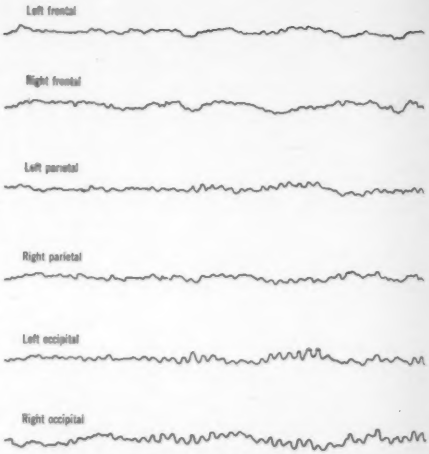

Fig. 5. *(Case 13)* Pick's atrophy. Low-amplitude, poorly organized record. Basic frequency is in alpha range.

Case 12. A 51-year-old woman was admitted October 5, 1952. Considered neurotic for several years prior to the onset of obvious symptoms of mental illness, she developed paranoid ideas concerning a physician who was treating her. She apparently had visual hallucinations as well.

On admission to the hospital, the patient was affectively flat, superficial, withdrawn, and paranoid. A diagnosis of involutional psychosis, paranoid type, was made, and she received a brief course of electroshock therapy which was terminated because of resulting confusion. She subsequently improved and was able to live on an open ward. Several months later, she was found wandering about the grounds in a confused state and, at this time, was referred to the neurology clinic. The patient was slow to follow directions and appeared bewildered, but no specific memory or language deficiency was found.

Examination of the spinal fluid was negative on 2 occasions. A pneumoencephalogram made July 14, 1953, showed slight increase in the size of the ventricles and sulci of the frontal and central areas—"findings suggest the possibility of a moderate degree of cortical atrophy."

An electroencephalogram showed low voltage, very poorly organized rhythm in the alpha range, and equivocal increase of the theta range frequencies and was interpreted as "not definitely abnormal" (Fig. 5).

The patient rapidly deteriorated and died August 29, 1953, of bronchopneumonia.

Examination of the brain revealed "severe atrophy of the frontal lobes except the major part of the precentral gyrus, mild to moderate atrophy of the inferior parietal lobule, but not of the rest of the parietal, occipital or temporal lobes." A midsagittal section revealed "enlargement of the lateral ventricles and suggestion of atrophy in the anterior part of the corpus callosum." Histologic appearance was that of Pick's lobar atrophy with the cortex in the areas of atrophy showing degenerative changes with the appearance of a "spongy state." No senile plaques or neurofibrillary changes were seen in silver preparations.

Case 13. A 68-year-old woman was admitted January 3, 1952. A maternal aunt had died in a state hospital, and the patient's younger sister was also hospitalized at Agnews with senile psychosis. The patient had become forgetful and eccentric in 1948 after a gastrointestinal ailment. Her incapacity had gradually increased and, at the time of admission, she was extremely confused and euphoric and showed aimless restlessness. Her speech was characterized by perseveration and stereotopy.

An electroencephalogram was of low amplitude with scant occurrence of alpha frequencies and superimposed irregular, and, at times, spiky faster rhythms. Records on April 21, 1952, and January 13, 1953, were interpreted as "not definitely abnormal."

The patient died in February 1953 after 2 grand mal seizures within a twenty-four hour period. Atrophy of both frontal lobes of the brain occurred greater on the right and sharply demarcated from the precentral gyri. Histologic examination confirmed the diagnosis of Pick's atrophy.

An electroencephalogram was made on the patient's sister and proved to be almost identical. Permission for autopsy could not be obtained.

Case 14. A 42-year-old housewife was admitted November 1, 1948. She had become unusually religious after her husband's death five years previously. Recently she had become agitated and would sit and wring her hands. She was financially irresponsible and was observed eating food out of a garbage can. At admission, the patient was described as fully oriented. Her speech was relevant and coherent, her affect was flat. Hebephrenic schizophrenia was diagnosed. The patient became increasingly active and confused and showed no response to therapy which included electroshock treatment. A prefrontal lobotomy was done on August 23, 1951. The operative record states: " . . . . . the subarachnoid space is tremendous . . . . the brain tough and firm. . . . " The operation was terminated after the leukotomy was completed on the right side. The patient was extremely restless and confused, chewed ceaselessly on rags and clothing, constantly picked at things on the floor, and was sexually aggressive. Apparently in an attempt to reduce the constant activity of the patient, a leukotomy on the left side was done on November 18, 1953. A wedge of cortex was removed. The pathologist reported "acute and chronic neuronal changes and reactive mobilization of glial cells and neuronophagia. Silver preparations show no senile plaques or neurofibrillary changes."

An electroencephalogram was obtained on December 16, 1952 during the interval between the lobotomy procedures. Although, at this time, the patient had regressed to the status of almost animal-like behavior, the electroencephalogram showed a normal-amplitude, fairly well-organized 10 cycle alpha rhythm throughout the recording. The only definite abnormality was a random, relatively low voltage 4 to 5 cycle slowing from the right anterior quadrant. This was attributable to the leukotomy done sixteen months earlier.

The patient died September 14, 1958, ten years after admission. The brain weighed 1,090 gm. Symmetric areas of atrophy were found in the frontal and temporal lobes. Atrophy was more pronounced in the frontal regions. The pathologist's diagnosis was Pick's disease.

DISCUSSION

All cases of Alzheimer's atrophy showed electroencephalographic abnormalities—usually a random, generalized slowing. Paroxysmal dysrhythmia was a superimposed abnormality in 4 Alzheimer records, and focal slowing occurred in 5 patients. In patients with focal slowing, the abnormality of the background rhythm and the fact that the location of the focal changes varied when serial recordings were obtained served to differentiate from localized pathology such as neoplasm. However, our practice has been to proceed with diagnostic studies such as arteriography or pneumoencephalography when focal changes are present in the electroencephalogram. A further observation in this regard is that the location of the focal slowing does not always coincide with the areas of greatest abnormality reported by the pathologist.

Contrary to expectation, the cases of Pick's atrophy showed no focal abnormality in the electroencephalographic tracings. They showed less evidence of generalized abnormality.

After review of many patients with presenile atrophy seen in the hospital population here, our impression has been that the degree of abnormality demonstrated in the electroencephalographic tracings generally correlates with the rapidity of progression of the illness at the time, rather than the specific histologic changes. This is in accord with the electroencephalographic findings in other disorders. Nevertheless, it was surprising that the cases of Pick's atrophy revealed so little electroencephalographic abnormality when personality and intellect were profoundly deteriorated.

On the other hand, all cases of Alzheimer's atrophy showed abnormality in the electroencephalographic pattern. The characteristic random, disorganized slowing seems to be readily distinguishable from the slowed, but rhythmic and essentially well-organized, electroencephalogram seen in normal older age groups and in some hypometabolic states. The electroencephalographic changes are not different, however, from those seen in the mentally disorganized, senile psychotic patient in whom a generalized cortical atrophy is also present. The electroencephalogram may be helpful in the early diagnosis of Alzheimer's atrophy but may miss Pick's atrophy.

ACKNOWLEDGMENT

The author wishes to acknowledge the able assistance of Mrs. Margaret Trammell in the preparation of this report.

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Effects of changes in composition of plasma on pial blood flow

I. Lipids and lipid fractions

John S. Meyer, M.D., and Arthur G. Waltz, M.D.

OUR EXPERIENCE has been that, occasionally, patients with insufficiency of the vertebral-basilar or carotid arterial systems relate the development of transient or permanent ischemic episodes to the ingestion of a heavy meal, often rich in fat, some hours earlier. In addition, we have rarely seen other patients who had developed symptoms of cerebral circulatory insufficiency during diabetic ketosis and hyperlipemia, which promptly subsided when the acidosis was controlled by insulin.

Other investigators have shown that the addition of high molecular weight substances, including dietary lipids, to blood in vitro or in vivo has profound effects on the properties of blood. In smears and suspensions of peripheral blood, there is aggregation of erythrocytes, rouleau formation, increased viscosity, and increased sedimentation rate.[1–6] In small vessel networks, such as the mesentery of the rat, the cheek pouch of the hamster, or the bulbar conjunctiva of man, flow is slowed, with aggregation of blood elements, particularly of erythrocytes.[3,5–8] In addition, dietary lipids have been reported to have effects upon the mechanisms of coagulation, with a tendency toward hypercoagulability.[9–15]

In an attempt to gain a better understanding of the pathogenesis of cerebrovascular symptomatology and to aid in the development of methods of prevention, we have made observations of the acute effects of lipids upon the flow of blood in the pial vessels. In a second paper, the effects of different substances of high molecular weights and of hypotonic and hypertonic solutions will be described.[16]

METHODS

In this part of the study, observations were made on 25 cats, 2 monkeys (Macaca rhesus), 2 rabbits, and 3 hamsters. The animals were fasted, except for sugar and water, for twenty-four hours prior to each experiment. Light anesthesia was induced by intraperitoneal injection of pentobarbital in an average initial dose of 30 mg. per kilogram of body weight, plus occasional supplemental intraperitoneal or intravenous doses, since many experiments were continued for six or more hours. Tracheostomy and esophagostomy were performed, and a polyethylene catheter was passed through the esophagus into the stomach and tied into place after its position had been confirmed by auscultation. The animal was then placed in a headholder of appropriate size, and both cerebral hemispheres were exposed. In all animals but the hamsters, the right middle cerebral artery was identified and occluded with McKenzie silver clips; in 1 rabbit, several branches of the middle cerebral artery were occluded, the main trunk not being exposed. The pial surface was protected by a covering of mineral oil or immersion oil warmed to body temperature.

A polyethylene catheter was inserted through the femoral artery into the abdominal aorta, and the blood pressure was recorded continuously by means of a Statham strain gage and an Offner type D electroencephalograph. The catheter was kept open with a solution of 3.2% sodium citrate. A separate polyethylene

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catheter was placed through the femoral vein into the inferior vena cava for removal of serial blood samples and intravenous injections.

The pial circulation was observed and photographed through a macrophotography system consisting of a 35 mm. Praktina single-lens reflex camera, a long extension tube with bellows, a rack-and-pinion focusing device, and a single photographic lens. For low-power photographs, either a Zeiss Tessar 50 mm. lens or a Zeiss Flektagon 35 mm. lens was used. These gave magnifications at the film of 7x and 10x, respectively, or magnifications of 56x and 80x on an 8 x 10 in. print. The lenses were reversed to minimize distortion. For high-power photographs, a Leitz Ultropak incident light illuminator was used with a single 11x objective lens and dipping cone, which was immersed in the mineral oil that covered the brain. The Ultropak gave a magnification of 30x at the film or 240x on an 8 x 10 in. print. Illumination was provided by stroboscopic electronic flash units firing on the brain or, in the case of the Ultropak system, through the side-arm condenser.

High-power photographs generally were taken of the right cerebral hemisphere in the area made ischemic by occlusion of the middle cerebral artery. Low-power photographs were taken of the left cerebral hemisphere with intact circulation. Anscochrome, Kodak Plus X, or Kodak Panatomic-X films were used.

After the preparation had stabilized, the steady state was observed and photographed. An initial blood sample of 1.8 cc. was drawn from the inferior vena cava via the polyethylene catheter placed into the femoral vein, thus minimizing any effects of tissue juice. The sample was added to 0.2 cc. of 3.2% sodium citrate in a siliconed test tube and gently mixed. The catheter was then flushed through with 0.5 cc. of 3.2% sodium citrate to assure patency. Part of the citrated whole blood was immediately placed in a Wintrobe hematocrit tube for determination of the erythrocyte sedimentation rate. Additional blood was immediately smeared on a clean glass slide and covered with a cover-slip. This was examined with a Bausch and Lomb dark-field illuminator and microscope for the presence of rouleau formation and chylomicrons. Photographs of the blood smears were taken with a Bausch and Lomb microscope camera and Kodak Tri-X film.

After one hour, the erythrocyte sedimentation rate was read and later corrected to a hematocrit of 40%. The sample was centrifuged at 3,000 rpm for thirty minutes, at which time the hematocrit and plasma turbidity (grade 0 to 4) were determined. The plasma was then decanted, and clotting studies were performed.

Studies of the coagulability of the blood were performed on fresh plasma or on plasma that had been fresh-frozen and stored for twenty-four hours. The plasma recalcification time (P.R.C.T.) was determined by adding 0.1 cc. of 0.85% sodium chloride solution and 0.1 cc. of M/40 calcium chloride to 0.1 cc. plasma at room temperature in a siliconed tube and rotating the tube every fifteen seconds until clotting occurred. The Russell viper venom (Stypven) time (R.V.T.) was determined by adding 0.1 cc. of 1% calcium chloride and 0.1 cc. Stypven (Burroughs, Wellcome, and Co., preparation of thromboplastic viper venom) to 0.1 cc. of plasma in a siliconed tube. All materials and glassware were warmed to 37° C. The mixture was then observed for the formation of fibrin, which was taken to be the end point.

After the initial steady-state determinations had been made, the experimental variable was introduced. In 16 cats and all the other animals, this consisted of an intragastric feeding of a mixture of whipping cream and butter by slow drip through the esophagostomy tube. The feeding was calculated to provide approximately 10 gm. of butterfat per kilogram of body weight. In addition, 2 cats were given an equivalent volume of skim milk (butterfat removed), and 5 cats were observed without the administration of any fluid. These 7 cats constituted the control group; 2 of the 5 cats not given any intragastric feeding were observed for a period of four to six hours and then were given a lipid suspension prepared for intravenous infusion (Lipomul) through the catheter placed in the femoral vein. The remaining 2 cats were given a slow intravenous infusion of a lipid phosphatide fraction prepared from soybeans (Asolectin).

After the introduction of lipid or other material, the pial circulation was observed and

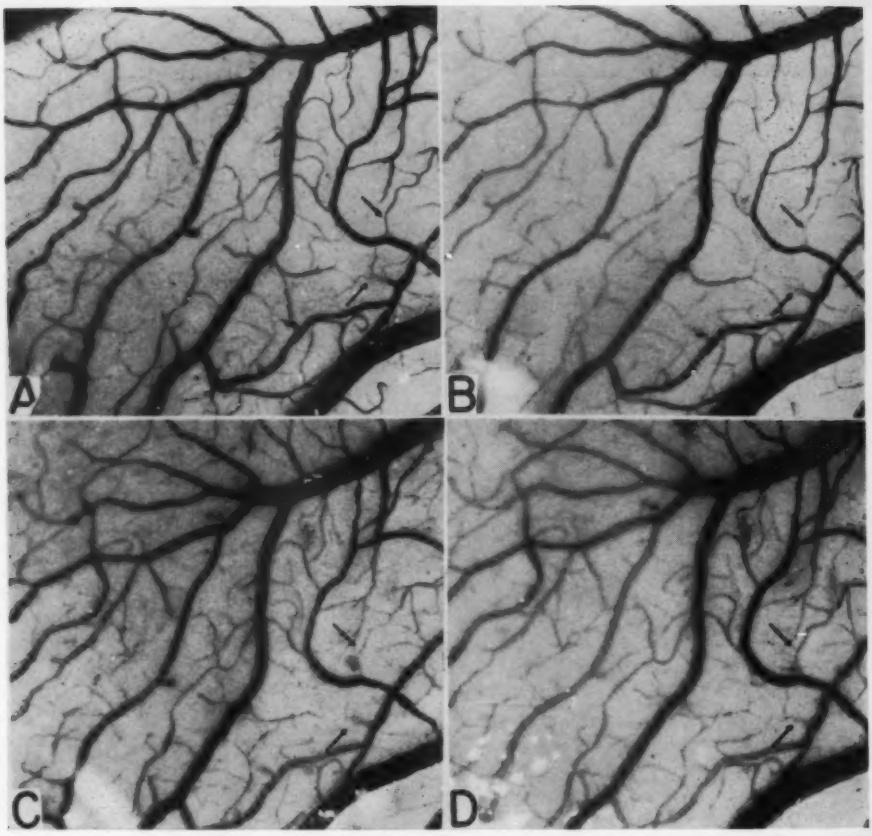

Fig. 1. Changes in the pial circulation up to six hours after occlusion of the middle cerebral artery and administration of intravenous Lipomul. (A) One hour after occlusion of the middle cerebral artery. (B) Three hours after occlusion. (C) Six hours after occlusion. (D) Two hours after the infusion of 30 cc. of Lipomul intravenously. Note restoration of small vessels and increase in width of arterioles. (× 41)

photographed at intervals of thirty to sixty minutes, up to a total of six to eight hours. Venous blood samples were usually drawn at intervals of two, four, and six hours, and the battery of tests was repeated. The blood pressure was continuously recorded to eliminate possible effects of hypotension.

RESULTS

Changes in Pial Circulation

Control animals. In 5 experiments with cats in which the preparations were observed without introduction of lipid, occasional narrowing of arterioles and disappearance of small vessels in the capillary bed were observed after three to six hours (Fig. 1). There was, however, no increase in aggregation of erythrocytes compared to the initial observations, and stasis or segmentation of the blood columns did not occur, provided the blood pressure was maintained. Comparable findings were observed on both ischemic and nonischemic hemispheres.

Similarly, there was no aggregation of blood elements when skim milk was given intragastrically. Narrowing of vessels on the arteriolar side and reduction of the vascular network

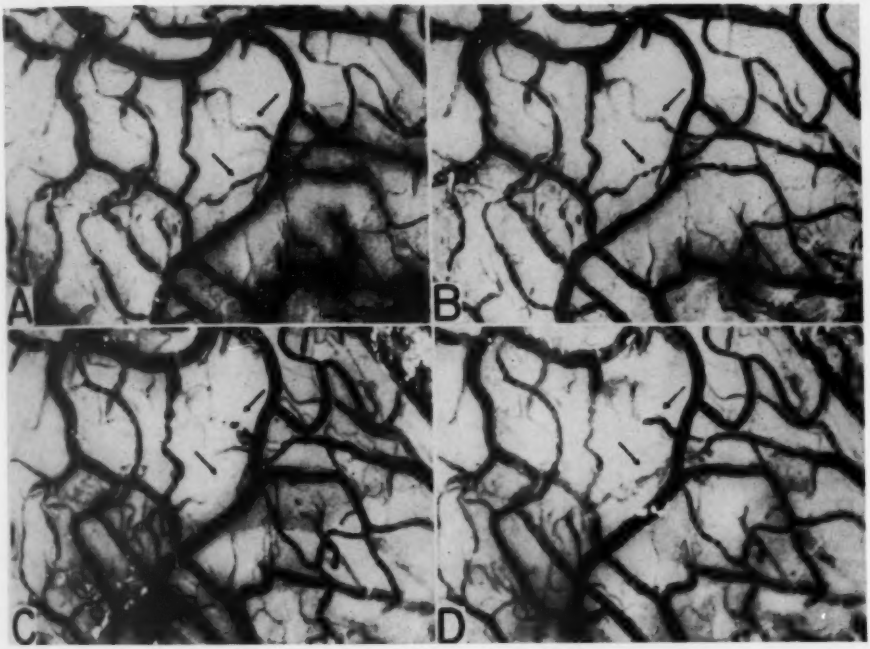

Fig. 2. Intravascular aggregation and segmentation of erythrocytes of the pial circulation of the cat after an intragastric fat meal. The middle cerebral artery had been occluded. (A) Before fat. (B) Two hours after the administration of butterfat, 10 gm. per kilogram, by gastric tube. Note early segmentation. (C) Five and one-half hours after fat; segmentation is more marked. (D) Six hours after fat (× 17)

was not seen, however, after the introduction of skim milk for periods of observation as long as eight hours.

Animals given butterfat. One to two hours after the intragastric feeding of butterfat (approximately 10 mg. per kilogram of body weight), aggregation of erythrocytes was discernible within the pial blood vessels. Intravascular erythrocyte aggregation began first with the development of a granular or particulate appearance of the columns of blood in the small venules and arterioles (approximately 20 to 60 μ). This was accompanied by slowing of the rate of flow of the blood. Such changes in the blood reached a maximum four to six hours after the administration of fat. In intermediate stages, there was further slowing of the rate of blood flow with a tendency of the leukocytes to margination. In advanced stages, larger masses or aggregates of erythrocytes showed intermittent stasis and were separated by clear spaces in which plasma flowed slowly (segmentation of flow). Slowing of flow might progress and rarely terminated in complete stasis, at which point cyanosis of venules with stagnation of the columns of blood occurred. Such changes were observed both in areas rendered ischemic by occlusion of the middle cerebral artery (Fig. 2) and in comparable areas of the nonischemic hemisphere (Fig.3), although the changes were consistently more marked in ischemic regions.

The changes produced by alimentary lipemia were similar to those seen in ischemic areas when infarction is produced by hypotension, but with certain notable differences. The changes were never as profound, and there was no preceding cyanosis of terminal venules. Aggregation of erythrocytes was generalized in

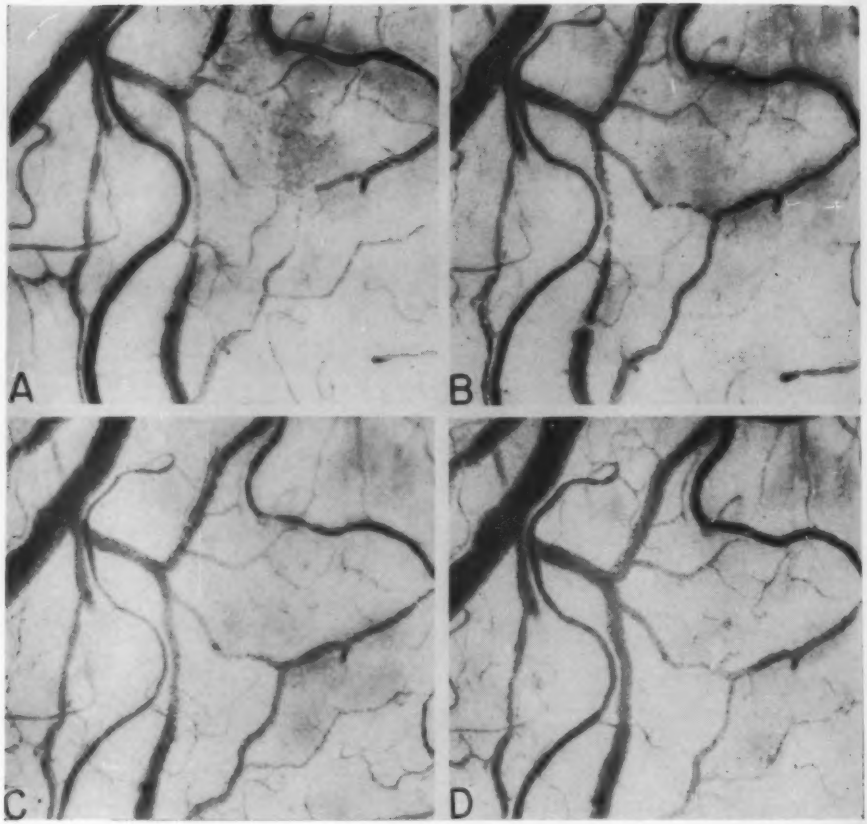

Fig. 3. Effects of butterfat on the pial circulation in an area not rendered ischemic (the middle cerebral artery had not been occluded). (A) Pial circualtion prior to fat. (B) Two hours after the administration of butterfat, 10 gm. per kilogram, by gastric tube. (C) Four hours after fat. (D) Six hours after fat. Note that changes are less pronounced and more transient than in Figures 6 and 7. (× 43)

association with lipemia, but segmentation was regional, occurring in certain vessels only and in different vessels at different times. When segmentation occurred, aggregates of erythrocytes were usually orange-red in color, rather than being dark blue or blue-black, as is seen with ischemic infarction.[17,18] This was particularly true if some blood flow was maintained, for, when stasis occurred, cyanosis of the aggregated erythrocytes followed.

During the eight hours of observation, there rarely occurred other events that are common in severe ischemic infarction, such as perivascular and diapedetic hemorrhages, the formation of platelet thrombi, emboli, and cerebral edema.

We were unable to detect any significant species difference in the changes induced in the pial circulation by alimentary lipemia among cats, monkeys, rabbits, and hamsters. It was not possible to observe the duration of these changes in the suspension stability of the blood resulting in erythrocyte aggregation and slowing of blood flow induced by the intragastric administration of fat, since the animal preparation could not be maintained intact

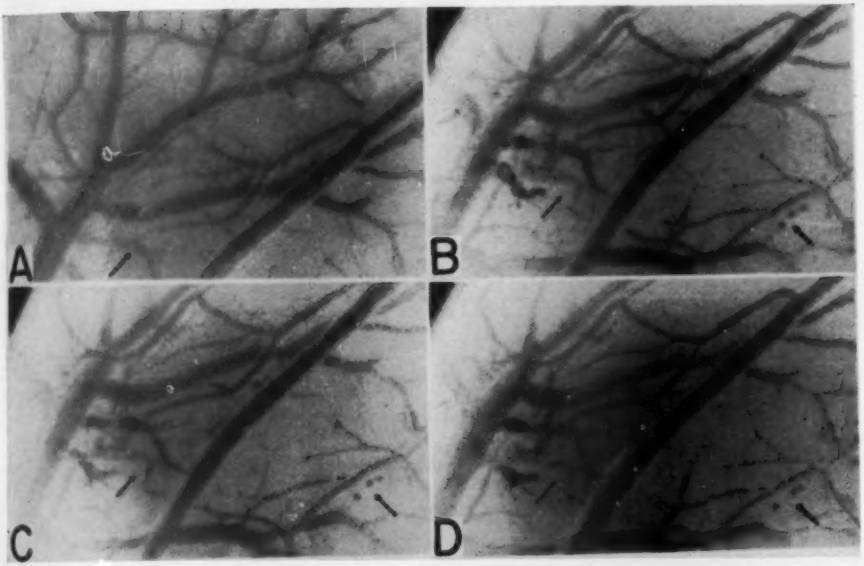

Fig. 4. Heparin fails to influence the changes induced by a meal of butterfat. (A) Pial circulation of the monkey following occlusion of the middle cerebral artery. No fat has been given. (B) Three and one-half hours after the administration of 10 gm. per kilogram of butterfat by gastric tube and fifteen minutes after the intravenous injection of 10 mg. of heparin. Note marked segmentation and stasis. (C) Twenty-five minutes after heparin. (D) One hour after heparin (× 17)

for longer than eight to ten hours. Hypotension with infarction or respiratory failure usually terminated the experiment before intravascular aggregation was observed to resolve.

Attempts were made on several occasions to reverse the aggregation that had occurred in small vessels after the feeding of fat by an intravenous injection of heparin through the catheter placed in the femoral vein. Up to 1,000 units (10 mg.) of heparin was given without significant results (Fig. 4).

Intravenous lipid and lipid fractions. After 2 preparations were observed for six hours, a commercial emulsion of 15% cottonseed oil prepared for intravenous use (Lipomul) was infused slowly intravenously. A total amount equivalent to approximately 1 gm. of cottonseed oil per kilogram of body weight was used. Despite the production of marked lipemia (Fig. 5), there was no aggregation of blood elements, segmentation, or slowing of flow (Fig. 1) during observation for the following three hours. The brain and blood were observed to be pale and creamy in color during this period.

Intravenous infusions of a 5% suspension of a phosphatide (Asolectin) were given to 2 animals. This material is a partially purified fraction prepared from soybeans. The phosphatide was suspended in 0.85% sodium chloride, and a quarter of the estimated blood volume was injected (approximately 0.7 gm. of phosphatide per kilogram of body weight). The changes following the intravenous administration of this material were similar to those seen following the intragastric administration of butterfat (Fig. 6).

Changes in the peripheral blood. Following the intragastric administration of fat and the intravenous infusion of lipid or phosphatide, peripheral chylomicronemia increased, as observed by dark-field microscopy. This chylomicronemia was evident within two hours after the intragastric feeding of butterfat and

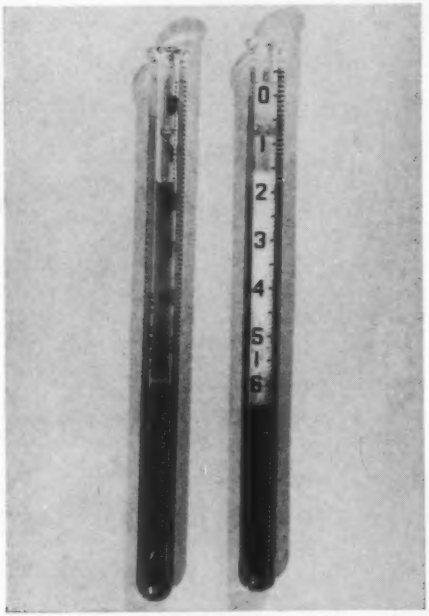

Fig. 5. Showing plasma turbidity after centrifugation. (*Left*) Before the intravenous infusion of Lipomul. (*Right*) After Lipomul injection. Note the opacity and creamy white appearance of the plasma.

immediately followed the intravenous administrations. The changes in the pial circulation correlated well with the degree of chylomicronemia, and, in 2 cats in which absorption of the fat was interfered with by gastric retention or diarrhea, neither chylomicronemia nor circulatory changes were prominent. Because of brownian movement, chylomicrons could not be photographed except after the intravenous injection of lipid (Fig. 7E).

Plasma turbidity closely parallelled the presence of chylomicronemia, as might be expected, although estimations of lipemia and chylomicronemia from plasma turbidity were not as accurate as the direct microscopic examination of peripheral blood (Table 1).

It was difficult to compare rouleau formation in different smears of blood. Frequently, there was an increase in the percentage of erythrocytes found in rouleaux after the intragastric administration of butterfat or the intravenous injection of phosphatide, but this was noted in animals given skim milk or nothing. In addition, in these experiments, rouleau formation was frequently observed to be moderate to marked in initial blood samples drawn before the introduction of the experimental material. It is noteworthy, however, that rouleaux were not observed following the intravenous injection of cottonseed oil emulsion (Fig. 7E).

The hematocrit did not vary appreciably during the course of any experiment. The maximum change was 3 to 4% and was not necessarily in the expected direction. For example, an increase in hematocrit from dehydration did not appear in the animals given nothing nor did a decrease in the hematocrit appear in those animals that were administered intravenous fluids.

The corrected erythrocyte sedimentation rate did not increase significantly after the intragastric or intravenous administration of lipid or phosphatide. The P.R.C.T. and the R.V.T. likewise did not show consistent or significant change following lipid administration. Any changes that did occur were variable and usually were within the limits of error of the technics used (Table 2).

DISCUSSION

The experimental observations reported here indicate that changes in blood flow occur in small cerebral vessels during the state of lipemia that follows a large meal rich in fat. The amount of fat used in these experiments, 10 gm. per kilogram of body weight, was purposely made larger than that in meals normally ingested by the animals studied in order to produce maximal effects. Under the circumstances, increased aggregation of erythrocytes with subsequent slowing of blood flow appears first in arterioles and venules of 20 to 60 μ in size an hour after the ingestion of fat and may progress up to the fourth hour, after which aggregation tends to remain unchanged or to diminish. If pronounced aggregation of erythrocytes occurs, segmentation of flow is seen in small vessels with a stream of clear plasma separating the aggregated masses. This change occurs in areas of otherwise intact blood flow but is consistently more marked in areas of

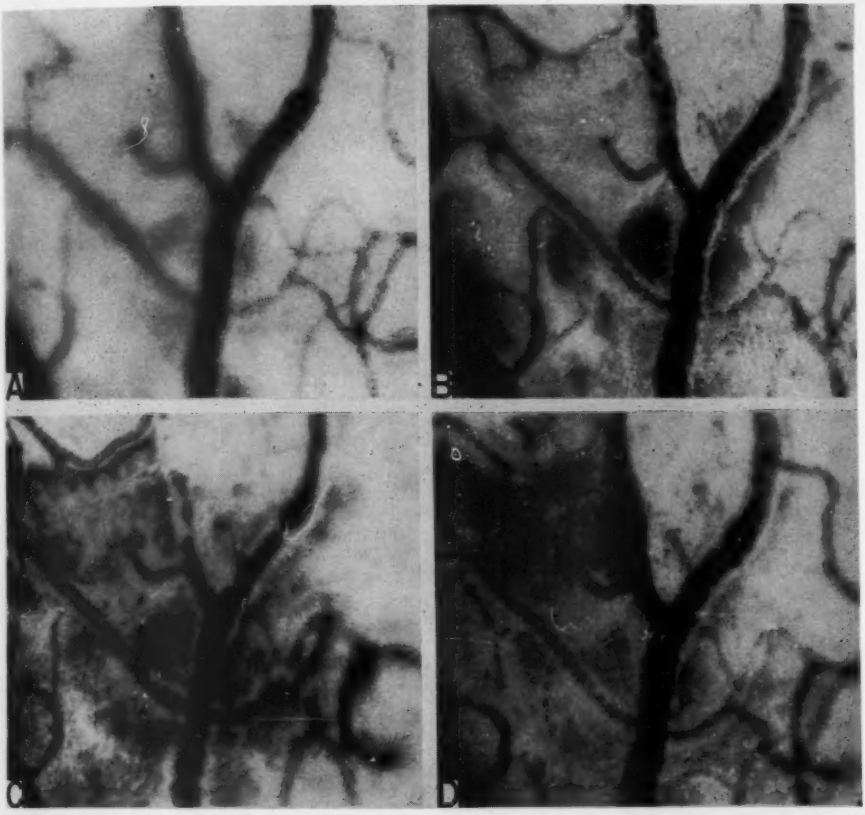

Fig. 6. Effects of Asolectin, a soybean phosphatide, on the pial circulation. (A) Pial circulation in an area made ischemic by occlusion of the middle cerebral artery. (B) After the intravenous administration of a 5% solution of Asolectin. Note the aggregation of erythrocytes. (C) One-half hour after the infusion. Note segmentation and stasis. (D) One hour after the infusion (× 135)

relative ischemia, that is, in the area of supply of an occluded middle cerebral artery.

Such changes in blood flow in small vessels differ from those seen following infarction caused by anoxic or ischemic anoxia, since the aggregation of erythrocytes appears to precede the slowing of blood flow. Initially, the aggregates of erythrocytes are orange-red in color rather than dark blue. Furthermore, in ischemic anoxia, the process is limited strictly to the territory of the occluded artery and always begins on the venous side of the capillary net.[17,18] The 2 processes of ischemic aggregation and postalimentary erythrocyte aggregation appear to be mutually synergistic, however, and, after a large fat meal, an ischemic territory formerly compensated by an adequate collateral circulation is liable to decompensate with resulting segmentation and stasis followed by cyanosis. Eventually, infarction may result. In a few experiments, not illustrated here, an additional small fall in blood pressure to 90 to 100 mm. Hg systolic several hours after the administration of fat produced extensive infarction of a degree not usually seen in the absence of fat, unless the blood pressure is reduced to much lower levels.

Intravascular aggregation of erythrocytes ap-

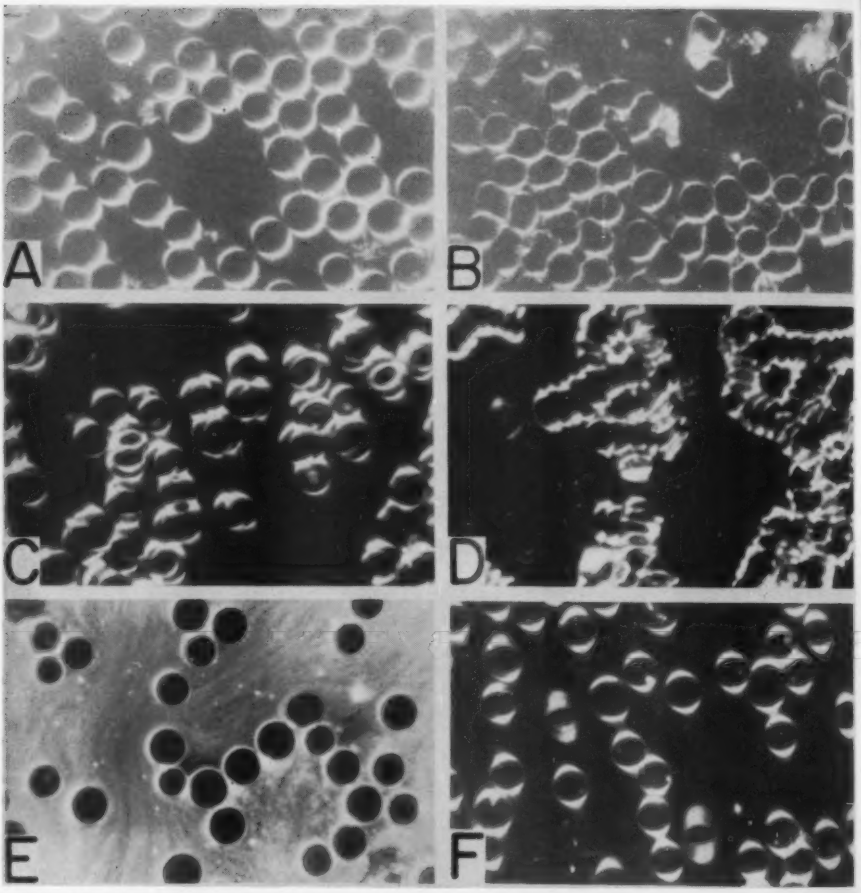

Fig. 7. Representative dark-field photomicrographs of smears of peripheral blood. (A) Sample drawn one hour after occlusion of the right middle cerebral artery. No rouleaux are present in the field. (B) Sample drawn six hours after occlusion. No fat was given. (C) Sample drawn two hours after the intragastric administration of skim milk. (D) Showing rouleaux formation in a sample drawn four hours after the intragastric administration of butterfat. (E) Sample drawn after the intravenous administration of Lipomul. Note the opacity of the plasma and streaming of chylomicrons. (F) One hour after intravenous administration of albumin (× 930)

pears to be the result of the absorption of lipid into the blood stream, since it correlated well with the appearance of chylomicronemia and turbidity of the plasma. It does not appear to be due to ischemia resulting from shunting of blood to the gastrointestinal tract, since there was no fall in blood pressure during or within the first hour after administration of butterfat given by a slow intragastric drip. The phenomenon was also delayed in its appearance following the administration of butterfat and did not occur when a similar volume of skim milk, containing 0.25 gm. total fat but having an equal amount of nonfat milk solids, was given in a similar manner. Aggregation of erythrocytes does not appear to be an artifact

TABLE 1

PERIPHERAL BLOOD STUDIES: INTRAGASTRIC BUTTERFAT

Animal and Sample	*Chylomicrons*	*Rouleaux*	*Hemato-crit*	*Corrected ESR*	*Turbidity*	*P.R.C.T.*	*R.V.T.*
FAC 15 (cat) 1.	1–4 per HPF	—	40%	51 mm./hr.	—	—	—
2. Fat—4 hr.	50–60	—	39	49	—	—	—
FAC 18 1.	0–1	90%	25	24	0	—	18 sec.
2. Fat—4 hr.	15–25	95	27	28	Tr	—	25
FAC 19 1.	0–1	70	31	1	0	—	18
2. Fat—4 hr.*	0–5	70	32	0	0	—	19
FAC 38 1.	0–3	85	37	13	0	4 min.	17
2. Fat—4 hr.	20–40	10	36	14	1+	4.5	19
3. Heparin	40–60	80	35	7	0	>30	>120
FAC 39 1.	0–2	90	17	20	0	5	27
2. Fat—4 hr.	80–100	20	23	16	Tr	3	21
FAC 40 1.	80–100	85	26	0	Hem**	2.5	30
2. Fat—2 hr.	80–100	70	23	0	Hem	3	28
FAC 41 1.	0	90	32	0	0	2.5	19
2. Fat—4 hr.	100–150	60	30	8	Tr	4	21
FAR 1 (rabbit) 1.	8–10	10	37	0	0	5	12
2. Fat—2 hr.	50–80	15	32	0	2+	2.5	10
FAR 2 1.	0–3	5	37	0	0	2	22
2. Fat—2 hr.	50–80	10	37	0	1+	2	18

1. Steady-state values 2. Values after fat administration
* Gastric retention: fat found in stomach at autopsy
** Hemolyzed

TABLE 2

PERIPHERAL BLOOD STUDIES: NO FAT; SKIM MILK; INTRAVENOUS LIPID; PHOSPHATIDE

Animal and Sample	*Chylomicrons*	*Rouleaux*	*Hemato-crit*	*Corrected ESR*	*Turbidity*	*P.R.C.T.*	*R.V.T.*
FAC 13 (cat) 1.	3–4 per HPF	0%	44%	1 mm./hr.	0	—	—
2. No fat—2 hr.	3–4	0	35	8	Hem*	—	—
3. Lipomul	Loaded	0	28	1	4+	—	—
FAC 14 1.	0–2	0	41	8	0	—	—
2. No fat—7 hr.	0–3	0	43	9	0	—	—
3. Lipomul	Loaded	0	42	0	4+	—	—
FAC 16 1.	0–1	5	38	18	0	2 min.	16 sec.
2. Skim milk—2 hr.	3–5	40	40	14	0	3	16
FAC 17 1.	0–4	90	33	5	0	6	30
2. Skim milk—4 hr.	0–3	100	36	12	0	5.5	32
FAC 45 1.	0–3	80	30	3	0	2.5	12
2. Asolectin—1 hr.	150–200	20	28	0	4+	2.5	**
FAC 47 1.	5–7	10	32	32	0	1.5	13
2. Asolectin—2 hr.	80–100	90	34	41	2+	1	12

1. Steady-state values 2. and 3. Experimental values
* Hemolyzed
** Too turbid to read end point

of prolonged exposure, since animals observed for six hours under similar circumstances but not given fat showed no aggregation of erythrocytes, although they did show some attenuation of pial vessels and reduction of the vascular net, probably due to dehydration with reduction of circulating blood volume. These vessels promptly returned to normal after the intravenous injection of Lipomul, and such changes did not appear in animals that were given skim milk, which supports the view that they were due to dehydration. Care was taken, however, to prevent dehydration or excessive blood loss, and serial hematocrits did not show significant evidence of either. Further evidence that the changes in the pial blood flow are due to postalimentary lipemia was afforded in 2 experiments in which fat was not absorbed. In 1 animal, the entire feeding was recovered from the stomach at autopsy, and, in the other, the feeding was expelled per rectum within thirty minutes. In these 2 experiments, there was no chylomicronemia or increased plasma turbidity nor were any changes observed in the pial blood flow.

INTRAVASCULAR AGGREGATION OF ERYTHROCYTES DURING POSTALIMENTARY LIPEMIA

Increased aggregation of erythrocytes tends to occur in areas of slowed blood flow, because turbulent flow results in increased frequency of collision of the erythrocytes. It has been shown in vivo that rouleau formation is enhanced by an increased frequency of collision of erythrocytes.[19] This factor would predispose areas of relative ischemia to intravascular aggregation, but, after fat absorption, the phenomenon appeared diffusely and in areas of intact flow. Nor can aggregation be due primarily to increased viscosity of the blood, which is known to occur following fat ingestion,[4] since the intravenous injection of Lipomul, which is a viscous solution, did not result in intravascular aggregation of erythrocytes.

Weis-Fogh[5] has made a detailed study of factors causing intravascular aggregation of erythrocytes. He reviewed 2 theories of its cause: [1] that it indicates a change in the suspension stability of erythrocytes identical with that which causes increase of the sedimentation rate or [2] that some "sticky substance" is adsorbed on the surface of the erythrocytes and increases their tendency to aggregate. Since the erythrocyte sedimentation rate in this series of experiments did not correlate with the changes observed in the pial circulation, the first theory must be rejected as an explanation for postalimentary intravascular aggregation. Observations of others have indicated that the so-called "sticky substance" responsible for the intravascular aggregation of erythrocytes actually results from adsorption of plasma colloids on erythrocytes following changes in nature and concentration of these colloids.[5,6]

The evidence reported here indicates that, after fat ingestion, lipid substances enter the blood stream, change the nature and concentration of the plasma colloids, and cause intravascular aggregation of erythrocytes. The lipid factor does not appear to be related to any physical properties of the chylomicrons. The intravenous injection of Lipomul produces particles of cottonseed oil, comparable in size and shape to those occurring naturally. In spite of this, if intravenous infusion of Lipomul is continued to the point at which the plasma is so loaded with chylomicrons that it becomes creamy white, aggregation of erythrocytes does not occur. It seems to be unlikely that glycerol is responsible for this effect; it has been used widely as an intravenous solution in animals and man without any reported changes in the blood.[20] We have not been able to correlate the changes in the pial blood flow after fat ingestion with any change in the coagulability of the blood as determined by the Stypven time or plasma recalcification time.

The absorption of lipid phosphatide fractions may be important in the causation of intravascular aggregation of the blood elements. We have found in these experiments that a phosphatide fraction prepared from soybeans produces intravascular aggregation of erythrocytes identical with that seen during postalimentary lipemia. It is possible, also, that unesterified fatty acids (UFA) may contribute to the tendency of erythrocytes to aggregate after a fat meal. It has been demonstrated that UFA are bound to the surface of erythrocytes soon after absorption[21,22] and may alter the repellent electric charge on the surface of erythrocytes. The absence of aggregation following the intravenous administration of Lipomul may be due to an absence of signifi-

cant amounts of phosphatide or of UFA in the artificially prepared emulsion. It would not seem to be related to the fact that Lipomul is a vegetable fat rather than an animal fat, since phosphatide produced from a vegetable source (soybeans) does produce aggregation. It is also unlikely that some transformation of lipid occurring during intestinal absorption is responsible, since the intravenous administration of soybean phosphatide resulted in the same changes as the intragastric administration of butterfat.

It is reasonable to assume that, if the ingestion of fat produces increased vascular aggregation of erythrocytes, the phenomenon should be demonstrable in vitro also. Others have reported that such changes do occur in vitro.[2-4] However, rouleau formation appeared in the peripheral blood smears of many of our control studies, and the correlation with in vivo changes was poor. In our experience, rouleau formation regularly appears if there is a delay in the preparation and examination of blood smears, and this method of assessing the tendency of erythrocytes to aggregate is unreliable. After the fat meal and intravenous injection of phosphatide, however, a tendency of erythrocytes to show distortion of shape when they separate from each other was observed in blood smears. This was not seen in control smears made prior to the administration of these substances. We believe this observation is a more valid indication of a tendency of erythrocytes to aggregate, since the phenomenon of distortion on separation becomes very marked after the intravenous injection of certain high molecular weight substances.[16]

Heparin is known to have a lipid-clearing effect, and it was considered possible that the injection of heparin might reverse the changes in the pial circulation induced by postalimentary lipemia. The injection of heparin produced no results. It is possible that the amount of fat given was too great to be cleared by heparin.

In 1 monkey recovering from occlusion of the middle cerebral artery, an attempt was made to induce an increased neurologic deficit by the intragastric feeding of 10 gm. of butterfat per kilogram of body weight. No change in the degree of hemiparesis was obserevd for four hours following the fat meal.

The observations reported here may be of importance in the consideration of therapeutic management of patients with cerebrovascular disease. Occasionally, elevation of fasting serum lipid and cholesterol levels are noted in these diseases. We have had under our care 4 patients who related the onset of their symptoms to the ingestion of a heavy meal; 1 had a fasting serum cholesterol of 335 mg. per cent, determined four days after the onset of symptoms of carotid artery insufficiency. He has now been maintained on a low-fat diet for eighteen months. His serum cholesterol has gradually decreased to 220 mg. per cent, and he has remained free of symptoms. Others have reported the provocation of symptoms of myocardial ischemia by a meal rich in fat[24] and the improvement of symptoms of myocardial and cerebrovascular ischemia by the use of a low-fat diet.[25] The experimental data reported here suggest that a diet low in fat may have usefulness in the treatment of cerebrovascular disease in preventing acute effects of aggregation and decreased flow of blood. This would be in addition to any benefit that a low-fat diet may have in the arrest of atherogenesis.[23]

CONCLUSIONS

1. Following the intragastric feeding of a meal rich in fat to experimental animals, increased aggregation of erythrocytes is visible within small pial vessels. Aggregation begins in small arterioles and venules with the appearance of orange-red clumps of erythrocytes. Aggregation may increase with resultant slowing of the flow of blood and segmentation of the columns of blood. Cyanosis appears only in the later stages.

2. In areas made relatively ischemic by vascular occlusion, postalimentary lipemia produces greater degrees of slowing and segmentation of blood flow than elsewhere in the brain. Stasis and rarely infarction may occur after a meal rich in fat.

3. Aggregation and slowing of blood flow due to postalimentary lipemia appear to be related to changes in the nature and concentration of plasma colloids. The lipid components causing circulatory changes appear most likely to be phosphatides or unesterified fatty acids.

4. The studies reported here indicate that a diet low in fat may have possible usefulness in the treatment of cerebrovascular disease.

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Results of long survival after thrombosis of the superior sagittal sinus

Orville T. Bailey, M.D.

For well over fifty years, it has been known that thrombosis of the superior sagittal sinus is regularly associated with severe hemorrhage and necrosis in the brain and that extension of the thrombosis into the superior cerebral veins is an important factor in determining the extent of injury. The condition was considered invariably fatal within a short time.

In 1933, Byers and Hass[1] presented convincing clinical evidence that some patients survive the initial phases of thrombosis of the superior sagittal sinus for months or even years and have severe mental and neurologic deficits during this period. In 1937, Bailey and Hass[2] described the pathologic findings in 3 such patients. The changes could be accounted for by lesions known to occur in recent superior sagittal sinus thromboses in stages of repair consistent with the period of survival. The clinical picture resembled acquired cerebral degeneration of childhood or "childhood encephalitis."

Since that time, a relatively small number of similar cases have been reported in the literature. This paper evaluates clinicopathologic correlations in the light of 3 additional personal cases and reports in the literature.

The detailed pathologic material on these 3 patients is published elsewhere.[3] Only brief outlines are given here for the purpose of comparison with those published in 1937[2] and other cases in the literature.

CASE REPORTS

Case 1. A 7-year-old boy was hospitalized because of loss of memory and motor deficit. Eight months before admission, he had had an acute illness, with sore throat and temperature of 101° F. This lasted for three weeks and was thought to be scarlet fever. On return to school, the patient took no interest in his work and had motor difficulty which prevented him from writing and from feeding himself. This condition persisted for three weeks. Rapid failure of memory became apparent and stereotyped movements of arms and legs appeared. The patient's condition gradually became worse, with the development of decerebrate rigidity, blindness, and extreme opisthotonos. The patient died three months after admission and eleven months after the acute illness.

Autopsy showed organized and canalized thrombi throughout the lateral sinuses and superior sagittal sinus, with extension into the superior sagittal veins; some deeper thrombi were present even in the deep cerebral gray matter. Destruction of the brain was very extensive throughout both hemispheres, somewhat less so in the deep cerebral gray matter, but was confined to edema and mild gliosis in the pons, medulla, and cerebellum.

Case 2. This girl was 5 years, 8 months old at death. Nine months before, she had become desperately ill with a high fever and a clinical picture regarded as encephalitis. This lasted for seventeen days; the temperature then returned to normal, and the general physical condition of the child improved. After that, she had intermittent but severe elevations of temperature, occurring about once a week. She made an incomplete recovery, gradually developing "cerebral palsy," then spastic quadriplegia, and finally, severe opisthotonos.

Autopsy showed organized and canalized thrombi in the superior sagittal sinus, transverse sinus, and superior cerebral veins, with destructive lesions in the cerebral hemispheres and deep cerebral nuclei. It is of some interest that, at the time of death, there was recent thrombosis of the canalizing channels in the sinuses and recent extension of the destructive cerebral lesions.

Case 3. This child was 6 years, 7 months old at death. She was a mongol who had had no other troubles until twenty months before death, when she developed acute illness with lethargy, then loss of power in the right arm and leg. This pro-

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Fig. 1. Extension of thrombus from the superior sagittal sinus into a superior cerebral vein. Note the hemorrhages and necroses in the adjacent cerebral cortex. There is also subarachnoid hemorrhage. Death thirty-nine hours after onset. (Hematoxylin-eosin × 26)

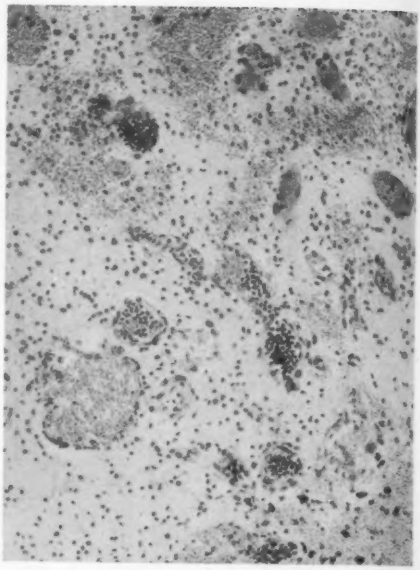

Fig. 2. Cortical necrosis and hemorrhage thirty-nine hours after onset of superior sagittal sinus thrombosis. Same case as Figure 1. (Hematoxylin-eosin × 160)

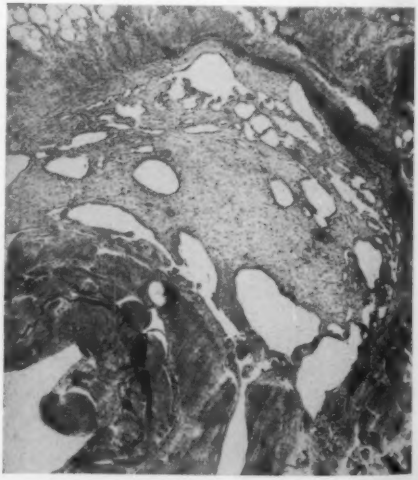

Fig. 3. *Case 3.* Organized and canalized thrombus in superior sagittal sinus twenty months after onset. (Hematoxylin-eosin × 9)

gressed rapidly until there was hemiparesis of the right side and the patient was no longer able to turn herself over or sit up. She gradually became very emaciated and unable to hold up her head or to take feedings; she died during an attack of measles.

At autopsy, a perforated appendix with peritonitis was found. The superior sagittal sinus was completely filled with organized and canalized thrombi, and destructive lesions throughout both cerebral hemispheres were extensive.

NATURE AND LOCATION OF LESIONS

From the standpoint of the neuropathologist, recognition of lesions resulting from thrombosis of the superior sagittal sinus and its tributary veins depends on evidence that the

changes found at autopsy can be accounted for by repair phenomena in lesions known to occur in patients dying a few days after thrombosis of those structures.

Although the lesions resulting from recent sinus thrombosis are fully described in textbooks and a few special publications,[4] there are some particular features which should be reemphasized. Thrombosis of the lateral sinus does not result in intracerebral damage unless there is extension of the thrombus into the superior sagittal sinus. When the thrombus begins in the superior sagittal sinus, however, intracerebral necroses and hemorrhages develop in a very high percentage of cases. Some degree of subarachnoid hemorrhage is almost always present.

The intracerebral hemorrhages and necroses vary a good deal in location and extent. As long recognized and as seen in the present material, their distribution and character depends on the extension of the thrombi into the superior cerebral veins (Fig. 1). The lesions are most severe when the veins draining into the middle third of the sinus are involved. Since the extension of thrombosis is nearly always bilateral, the lesions also are bilateral but often not symmetric.

Hemorrhages and necroses are found in the cerebral convolutions and extend beyond them into the deep cerebral white matter with some frequency. If the smaller tributaries of the superior cerebral veins are involved, hemorrhages and necroses appear in the basal ganglia (Bailey and Hass[4]). The cerebellum is rarely involved, and no instance of damage to the brain stem has been observed in the present material.

Histologically, the intracerebral necroses associated with recent thrombosis of the superior sagittal sinus are essentially infarctions of venous origin (Fig. 2). Some degree of hemorrhage is associated with the necroses in nearly all instances. This would be in accord with the view that hemorrhagic infarction occurs when there is some continued circulation in the area after the infarction has developed. In these lesions, the arteries are not occluded at the outset and would continue to bring blood to the region until secondary thrombosis takes place or they become occluded by other means.

The hemorrhagic necroses commonly extend to the pial surface, and rupture into the subarachnoid space occurs almost uniformly. Subarachnoid hemorrhage is seldom massive but usually is considerable. Cerebrospinal fluid obtained by lumbar puncture is strongly blood tinged, except in a few patients in whom lumbar puncture was performed very soon after onset[4]—further evidence that intracerebral necroses are the source of subarachnoid bleeding. While it is tempting to postulate rupture of the greatly distended and only partially thrombosed veins in the subarachnoid space, there is no definite evidence of this.

Fig. 4. *Case 2.* Organized and canalized thrombus in superior cerebral vein nine months after onset. (Hematoxylin-eosin × 80)

On the basis of these considerations, it is now possible to characterize the lesions to be expected when there is a sufficient period of survival for the cellular sequences of repair to dominate the histologic picture.

An organized and canalized thrombus in the superior sagittal sinus is essential to the diagnosis and was present in all the cases reported here (Fig. 3), as well as in those described in 1937.[2] When necroses occur within the cerebral parenchyma, organized and canalized thrombi can be found in the superior cerebral veins (Fig. 4). It is of interest that no such thrombi were found in Cases 1 and 2 of the 1937 report;[2] 1 small intracerebral necrosis

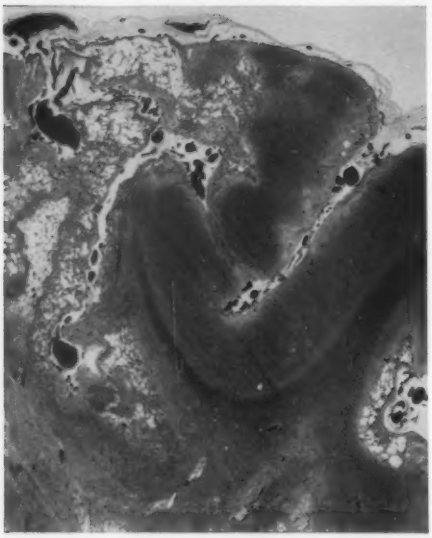

Fig. 5. *Case 3.* Multiple necroses in cerebral convolution with extension to deep cerebral white matter twenty months after onset of superior sagittal sinus thrombosis. Note the cystic appearance of the lesions and increased meningeal vascularity. (Weil's stain × 6)

was present in Case 1 and none in Case 2. In contrast, organized thrombi were found in the superior cerebral veins in Case 3 and in all 3 patients described in this report; in these 4 cases, intracerebral necroses were present. In Case 3 of the present series, organized and canalized thrombi were found deep in the basal ganglia, associated with infarction of this region. It is easy to overlook these thrombi, especially in the superior cerebral veins, because they tend to slip away from the plane of section, particularly in paraffin-embedded material. Such organized and canalized thrombi, however, would seem to be of prime importance in the production and distribution of the intracerebral lesions.

The characteristics of these lesions have been described elsewhere[2] and in detail in an excellent recent report by Courville.[5] They consist essentially of infarctions with repair. Thus, cyst formation occurs (Fig. 5), usually with compound granular corpuscles in the clear or yellowish fluid which fills the lumen. The cysts are surrounded by a thick feltwork of astrocytes, intermixed with newly formed capillaries. While occasional collagen fibers are seen, connective tissue participation in the repair is minimal. Usually, some hemosiderin in phagocytic cells is found.

Courville[5] has pointed out the presence of laminar necroses of the third to sixth cortical layers in the regions adjacent to the necroses and has attributed them to secondary ischemic alterations. This agrees completely with the findings in the present material. He also has pointed to the extensions in the subcortical white matter (Fig. 5).

The regions of involvement are located in the cerebral convolutions superiorly, while the basal cortex, brain stem, and cerebellum are spared, as attested by the distribution of lesions in patients dying soon after the onset of thrombosis. However, mild edema and gliosis of the brain stem is seen in some of the cases with long survival. Involvement of the basal ganglia is again in the form of hemorrhagic necrosis with repair.

Since the distribution of lesions should be the same as in patients dying soon after the onset of sagittal sinus thrombosis, the report of Dekaban and Norman[6] is puzzling. Their patient had an organized and canalized thrombus in the superior sagittal sinus, but the extent of involvement of the superior cerebral veins was postulated from the distribution of lesions rather than fully demonstrated histologically. The lesions in the cerebral hemispheres were confined to the left, the right cerebral cortex and basal ganglia being normal. The whole situation was complicated by a lesion of the cerebellum of a type not found in the present material, in our older material,[2] or in that of Courville.[5] The peculiar unilateral involvement, the cerebellar changes, and the lack of histologic definition of the extent of thrombosis in the cerebral veins make it difficult to evaluate this report. Possibly, the superior sagittal thrombosis was secondary to arterial or other cerebral disease.

Additional information on patients with longstanding thrombosis of the superior sagittal sinus is gained by study of the leptomeninges. Residua of the subarachnoid hemorrhages are easily identified by the presence of fine, dis-

persed collagen fibers, extending throughout the subarachnoid space superiorly, with maximal concentration over the areas of intracerebral involvement. Hemosiderin is abundant within the meshes of the tissue. Greatly distended veins are striking (Fig. 5). The basal meninges show mild fibrosis or none at all.

CLINICOPATHOLOGIC CORRELATIONS

At the present time, it is difficult to identify clinically the patients who have acquired cerebral degeneration of childhood on the basis of superior sagittal sinus thrombosis. The clinical sequences are an acute illness consistent with thrombosis of this structure, gradual and incomplete recovery, further progression of the mental and neurologic deficit, and development of mild or moderate hydrocephalus. The final phase is often characterized by decerebrate rigidity and opisthotonos.

The clinical findings in thrombosis of the superior sagittal sinus are well described, but the condition is much more often found at necropsy than diagnosed before death. This discrepancy suggests that the clinical syndrome in a considerable percentage of patients departs widely from the "typical" picture. If the diagnosis is not easy to establish when the patient is seen at the time of onset of the thrombosis, the difficulties are compounded when one attempts to make the diagnosis in retrospect, as is the case if the child is first seen in an advanced stage of mental and neurologic defect. The acute illness has been severe enough to be remembered and described by relatives in our cases, but diagnosis in any of them from the histories alone would have been hazardous. Another point adds to the confusion—some patients with recent thrombosis of the superior sagittal sinus succumb *without any recognized neurologic abnormality* (Bailey and Hass;[4] see especially Case 1). In such cases, blood in the spinal fluid may be demonstrated by a lumbar puncture performed only because no diagnosis could be established otherwise in a critically ill child. This situation is not unique to sagittal sinus thrombosis. For instance, severe acute anterior polymyelitis in a very young child occasionally is unaccompanied by overt neurologic changes initially.

After the acute illness, the patients who survive superior sagittal sinus thrombosis slowly improve but recovery is very incomplete; mental regression and usually some neurologic deficit occur. The improvement at this period would correspond pathologically to the stage of subsidence of edema around the necroses, resolution of hemorrhage, and such limited circulatory readjustments as are possible, including the development of canalizing channels in the thrombi. The deficit at the same interval would be due to irreversible loss of brain parenchyma.

This stage is followed by definite further mental and neurologic regression. The causes for this are probably many and as yet incompletely understood. There are 2 which seem well established at the present time. Laminar necrosis develops progressively in the third to sixth cortical layers in the portions of cerebral cortex beyond the original lesions, as pointed out by Courville[5] and discussed above. This process is a secondary one, resulting from progressive cortical ischemia. Second, repeated episodes of further thrombosis, as extensions of the old ones, occur in veins previously unoccluded and in canalizing channels of the old thrombi. Death accompanied such an episode in Case 2 of this report. The new thrombi were seen in canalizing channels, and there was fresh spread of the cerebral infarctions. This child had had repeated attacks of fever between the time of the acute thrombosis and death. These may have been related to other periods of thrombus extension.

In this period, mild to moderate hydrocephalus is often recognized when pneumoencephalograms are made. Russell,[7] in discussing 3 such patients in 1949, considered hydrocephalus a direct consequence of the sinus thrombosis. In a further study in 1954,[8] she reported 2 additional cases, 1 with ventricular dilation, studied particularly from the standpoint of hydrocephalus. Russell concluded that, in some instances, the enlargement of the ventricle is due to impairment of cerebrospinal fluid absorption and that, in others, it is a hydrocephalus e vacuo. Some cases of "otitic hydrocephalus" are the result of lateral sinus thrombosis with extension into the superior sagittal sinus and its tributary veins. The name applied to the condition by Symonds[9] focuses attention on this 1 feature of a complex clinicopathologic entity.

Neurologic changes in the patients are as varied as the location of the lesions. Convulsions are frequent; hemiplegia occurs in some but not all patients; and mental development not only ceases but regresses. In Cases 1 and 2 of this series, the terminal phases of the illness were those of decerebrate rigidity and, finally, severe opisthotonos, probably associated with progressive embarrassment of circulation in the brain stem, as attested by edema and mild gliosis in Case 1. In the presence of such extensive changes throughout the brain, specific correlations are not satisfactory.

INCIDENCE

Widely divergent views have been expressed in the literature on the incidence of this condition. They vary from the prediction of Byers and Hass[1] that many examples would be found to Courville's[5] emphasis on the extreme rarity of the condition. The actual incidence would seem to lie between these views.

The frequency of death from acute sagittal sinus thrombosis has been greatly reduced since 1933, when Byers and Hass made their estimate. It is reasonable to suppose that the number of patients who survive for long periods of time also has decreased.

The greatest difficulty in estimating the incidence of this condition is that it often is not searched for by neuropathologists. The superior sagittal sinus frequently is examined superficially or not at all at necropsy. Organized and canalized thrombi are not always easy to identify grossly, especially when the canalizing vessels are large enough to admit the point of dissecting scissors; only histologic sections are adequate to rule out these thrombi. Furthermore, the intracerebral lesions themselves are sufficiently characteristic to warrant special study of the sinus, if it has not been made previously. At this point, the dura may have already been discarded. It is significant that those most interested in the condition have identified the most cases (6 personal cases and 5 reported by Russell[7,8]).

Originally, the form of sagittal sinus thrombosis most likely to be followed by partial recovery and survival for months or years was thought to be the marantic type in poorly nourished, dehydrated infants.[1,2] The cases accumulated up to the present time, however, include more examples of lateral sinus thrombosis with extension into the superior sagittal sinus and its tributary veins. Lateral sinus thrombosis without such extension is not associated with intracerebral necroses and their attendant clinical consequences.

The clinical picture is one usually leading to the diagnosis of acquired cerebral degeneration of childhood or, if there are febrile episodes, "childhood encephalitis." It is among such patients that attempts should be made to establish more accurately the nature and incidence of this condition.

SUMMARY

1. Described are 3 patients who survived an initial attack of thrombosis of the superior sagittal sinus and its tributary veins, for eleven months, nine months, and twenty months, respectively.

2. The development and distribution of intracerebral hemorrhages and necroses are determined largely by the degree to which the superior cerebral veins are involved.

3. Progressive clinical deterioration is correlated with spreading laminar cortical necrosis resulting from increasing ischemia and with further episodes of thrombosis in the cerebral veins and in canalizing channels of the thrombi.

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Refractory and irresponsive periods of muscle in progressive muscular dystrophy and paresis due to lower motor neuron involvement

Thomas W. Farmer, M.D., Fritz Buchthal, M.D., and Poul Rosenfalck, M.Sc.

THIS STUDY was undertaken to determine the refractory and irresponsive periods of muscle fibers affected by progressive muscular dystrophy, peripheral nerve injury, and amyotrophic lateral sclerosis. Findings in normal subjects have been reported.[1]

METHOD

The method has been described in detail previously.[1] In brief, paired stimuli were delivered through a bipolar needle electrode inserted into the distal part of the muscle outside the end plate zone. Using different strengths of the testing stimulus, the *refractory period* was measured as the shortest time interval at which both the conditioning and the testing stimulus evoked action potentials. The time interval between these 2 action potentials, denoted as the *irresponsive period*, was measured as well.

The action potentials were recorded by means of a concentric needle electrode inserted 15 to 25 mm. proximal to the stimulating electrode. The strength of the conditioning stimulus and the position of the stimulating and recording electrodes were adjusted until an all-or-none response of short duration (1.5 to 6 msec) was obtained, indicating activation of 2 to 3 fibers.[2] The strength of the conditioning stimulus was usually 1.2 to 1.3 times threshold. The strength of the testing stimulus was increased stepwise from threshold to 2 or 3 times threshold. The absolute refractory and irresponsive periods were found when the strength of the testing stimulus was such that the time interval between effective stimuli and between the corresponding action potentials was shortest.

In all experiments, the intramuscular temperature, measured by 2 thermocouples inserted to lie close to the stimulating and recording electrode tips, was maintained at normal values by means of a heating pad placed under the muscle. This was of particular importance in paretic muscles, which frequently had a temperature below normal.

MATERIAL

Of the 11 patients with *progressive muscular dystrophy*, 5, 14 to 17 years of age, suffered from the generalized pseudohypertrophic type of the disease; 4 brachial biceps and 1 anterior tibial muscle were investigated. The restricted facioscapulohumeral or limb-girdle type of the disease was found in 6 patients 19 to 66 years of age; 3 brachial biceps, 1 deltoid, and 3 anterior tibial muscles were investigated. All patients had a family history of similar muscle disease, histories of chronic progressive muscular wasting, neurologic and electromyographic findings characteristic of progressive muscular dystrophy, and muscle

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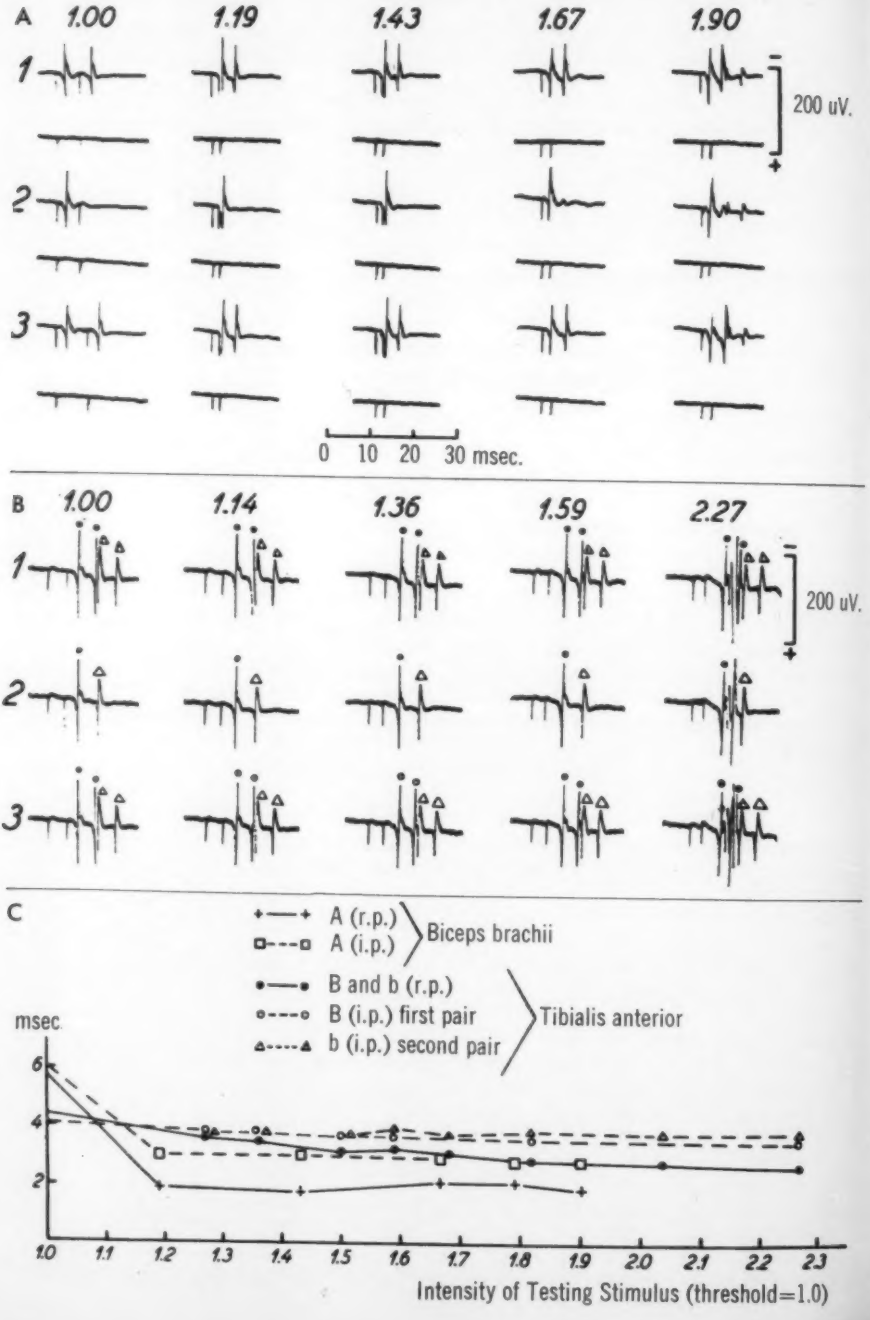
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C
A (r.p.)
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Biceps brachii
B and b (r.p.)
B (i.p.) first pair
b (i.p.) second pair
Tibialis anterior
msec
6
4
2
1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0 2.1 2.2 2.3
Intensity of Testing Stimulus (threshold=1.0)

Fig. 1. Progressive muscular dystrophy, pseudohypertrophic type. [A] Action potentials from a small group of muscle fibers evoked by direct stimulation in the brachial biceps. The figure above each column denotes the strength of the testing stimulus (threshold = 1.0) and the traces in each column show the shortest effective (1 and 3) and the longest ineffective (2) intervals between stimuli of a pair. The moments of stimulation are indicated on each trace and below each action potential record. (Repeat rate of paired stimuli, 1 per second; intramuscular temperature, 37° C.). [B] As in *A*, in the anterior tibial muscle; each stimulus activated 2 muscle fiber bundles marked O and △, respectively (intramuscular temperature, 35.6° C.). [C] Ordinate: refractory periods (r.p.) and irresponsive periods (i.p.) of the fiber bundles illustrated in *A* and *B*. Abscissa: strength of the testing stimulus.

biopsies consistent with this diagnosis. With one exception, the disease had lasted for more than ten years. Of the 12 muscles investigated, 6 had a force graded as 1 or 1+, 1 a force graded as 3+, and 5 a force indistinguishable or almost indistinguishable from normal (4+ or 5)—scaled according to the Medical Research Council.[3]

In 6 of the 8 patients with *peripheral nerve injury*, paresis was due to damage of the brachial plexus or the musculocutaneous nerve; 6 brachial biceps muscles were studied. In 1 patient, paresis was due to injury to the femoral nerve and the femoral rectus muscle was examined; in 1 with peroneal nerve injury, the anterior tibial muscle was examined. In 5 patients, paresis had lasted for five to seven months and, in 3, for less than two and one-half months. There were fibrillation potentials in 6 muscles. In the 2 muscles without fibrillation potentials, the injury had occurred seventeen days and five months previously. In 4 muscles, the paralysis was complete both clinically and electromyographically; in 4, the force was graded as 1 or 2.

In 4 patients with *amyotrophic lateral sclerosis*, 4 brachial biceps muscles were investigated. In addition, the anterior tibial muscle was examined in a case with *infantile progressive spinal atrophy* (Werdnig-Hoffmann type) and in a case with *peroneal muscular atrophy* (Charcot-Marie-Tooth). In all 6 patients, the disease had lasted for more than one year. The muscles were severely paretic (graded as 2 or 3), and 2 of the muscles from the patients with amyotrophic lateral sclerosis had, in addition to atrophy, a moderate degree of spasticity. There were fibrillation potentials in 5 muscles.

RESULTS

Progressive muscular dystrophy. The average refractory period was significantly shorter in progressive muscular dystrophy than in normal muscle. Figure 1*A* and *B* illustrate the determination of the shortest time interval at which both of the paired stimuli evoked action potentials. The action potentials were all-or-none, contained a positive-negative deflection lasting less than 150 μsec., and had a total duration in these cases of 1.5 and 3 msec. As in normal muscle, the voltage of the response evoked by the testing stimulus was lower than that of the conditioning action potential by no more than 15%. Each vertical column of Figure 1*A* and *B* shows the shortest time interval at which a given strength of the testing stimulus produced a response (lines 1 and 3) and the longest at which it did not (line 2). At a strength 1.9 times threshold (Fig. 1*A*), an additional action potential appeared without interfering with the determination of the refractory period of the main response. The absolute refractory period in this case was 1.8 msec., shorter than in normal muscle (2.2 to 4.6 msec.).

In muscles affected by progressive muscular dystrophy, the conditioning stimulus evoked 2 responses in 15% of the fiber bundles studied compared with a 2% incidence in normal muscle. The relative and absolute refractory periods of both potentials in the double response were identical; the irresponsive periods differed. An example of double responses is given in Figure 1*B*. The temporal dispersion between the 2 action potentials was sufficiently great to permit determination of the refractory periods of both potentials. In this case, the absolute refractory periods were 2.6 msec. and the irresponsive periods, 3.5 and 3.8 msec.

Refractory and irresponsive periods as a function of the strength of the testing stimulus are given in Figure 1*C* for the fiber bundles of *A* and *B*. Figure 2 contains the average plot of the 37 fiber bundles investigated and, for

comparison, the average values from 42 fiber bundles of normal muscle.

At all strengths of the testing stimulus, the refractory period of dystrophic muscle was significantly shorter than that of normal muscle. The absolute refractory period averaged 2.5 ± 0.1 msec. as compared with 3.6 ± 0.1 msec. in normal muscle. The absolute irresponsive period of dystrophic muscle averaged 3.5 ± 0.1 msec. and was the same as that of normal muscle (3.7 ± 0.1 msec.).

In both dystrophic and normal muscle, the refractory and irresponsive periods attained their shortest values when the strength of the testing stimulus was about 50% above threshold. In dystrophic muscle, refractory and irresponsive periods were identical at threshold; with increasing strength, the irresponsive period became progressively longer than the refractory. The testing stimulus could be increased to greater strength than in normal muscle without interference of action potentials from neighboring fibers; in 60% of the refractory period determinations, the testing stimulus could be increased to more than twice the threshold, as compared with 20% of the determinations in normal muscle.

As in normal muscle, there was a supernormal period[1] beginning 3 msec. after the conditioning stimulus, when the threshold of the testing stimulus was equal to the threshold of the conditioning stimulus (T_1, Fig. 2). The precise course and duration of the supernormal period were not investigated; 20 to 30 msec. after the conditioning stimulus, the threshold to the testing stimulus was lower than that to the conditioning stimulus by 15%.

The histograms of the absolute refractory and irresponsive periods of 38 muscle fiber bundles from the 11 patients with progressive muscular dystrophy are given in Figure 3. The absolute refractory periods ranged from

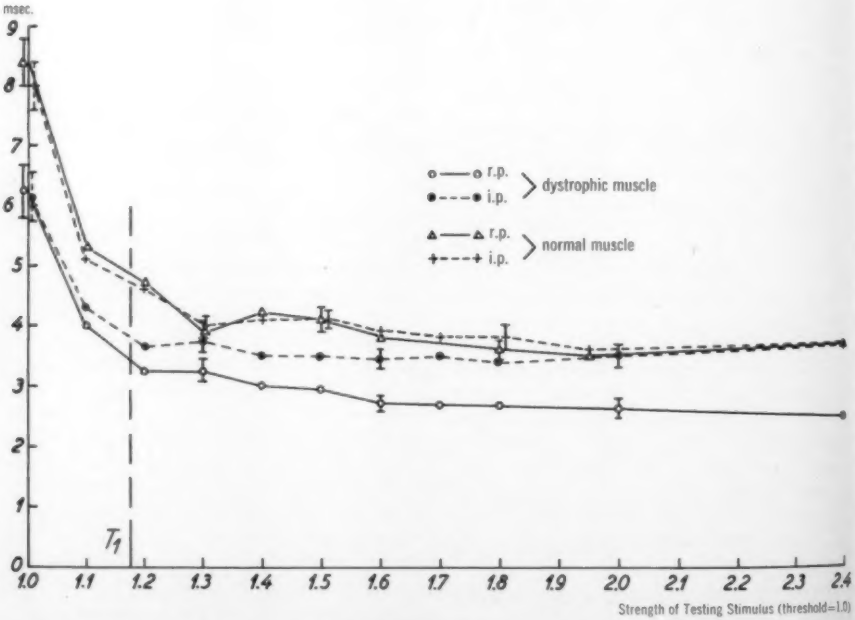

Fig. 2. Illustrating that the average refractory period in progressive muscular dystrophy is shorter than in normal muscle fibers and that the irresponsive period in dystrophic muscle exceeds the refractory period (37 fiber bundles from dystrophic and 42 from normal muscles). The vertical bars denote the standard error of the mean, and T_1 indicates the threshold strength of the conditioning stimulus.

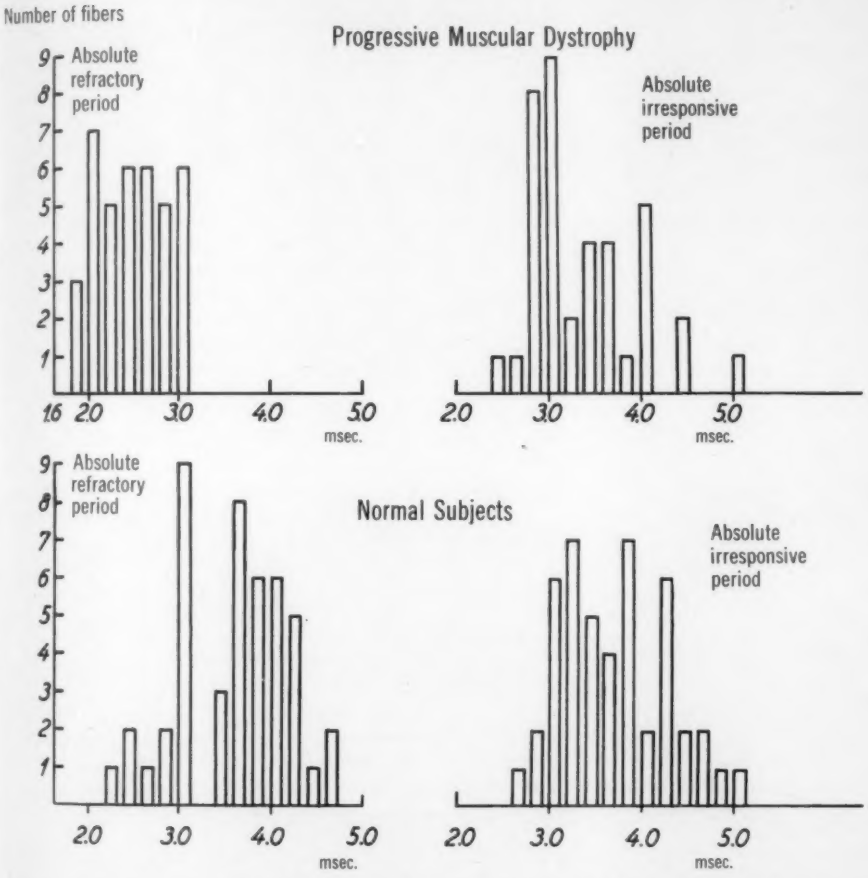

Fig. 3. Histogram of absolute refractory and irresponsive periods in dystrophic (38 fiber bundles) and in normal muscle (46 fiber bundles). Repeat rate of paired stimuli, 1 per second; intramuscular temperature, 34.5 to 37° C.

1.8 to 3.1 msec.; 15 of the 38 muscle fiber bundles had absolute refractory periods shorter than the lowest values found in normal muscle, and the rest corresponded to the group with short refractory periods in normal muscle.[1] No dystrophic fibers corresponding to the group with long refractory periods in normal muscle were noted.

The absolute irresponsive periods ranged from 2.4 to 5 msec., a range similar to that in normal muscle. In view of the short refractory period, this is evidence of a significant delay of the action potential evoked by the testing stimulus. The plot of the absolute irresponsive period as a function of the absolute refractory period (Fig. 4) shows the former to be the longer, in most cases by from 0.7 to 2.5 msec. In normal muscle, the longest delay of the second action potential was 0.4 msec.

With increasing repeat rate of the paired stimuli, the relative and absolute refractory and irresponsive periods increased (see table). This was also found in normal muscle; how-

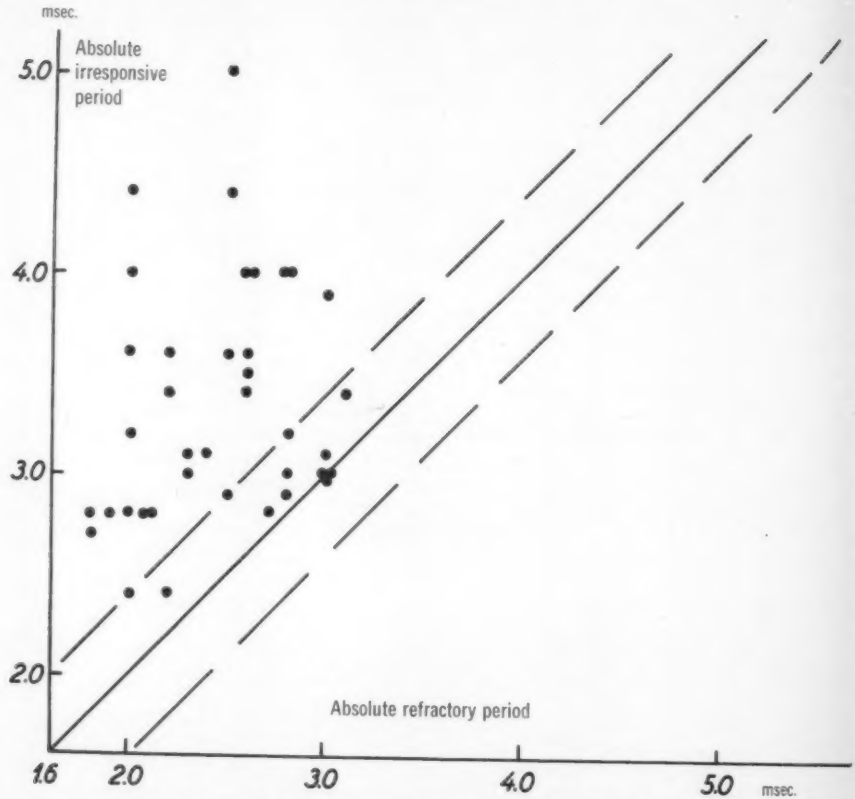

Fig. 4. Illustrating that the absolute irresponsive periods in dystrophic muscle exceed the absolute refractory periods. The broken lines correspond to the maximum difference between absolute irresponsive and refractory period of ± 0.4 msec. in normal muscle.

ever, 40% of the fiber bundles examined in normal muscle failed to respond to paired stimuli at a rate of 4 per second. In dystrophic muscle, only 1 of 11 fiber bundles failed to respond to repeat rates of 4 and 5 per second.

PROGRESSIVE MUSCULAR DYSTROPHY. ABSOLUTE REFRACTORY AND IRRESPONSIVE PERIODS AT DIFFERENT REPEAT RATES OF PAIRED STIMULI (36.5° C.)

Repeat rate of paired stimuli per second	*Number of muscle fiber bundles*	*Absolute refractory period (msec.)*	*Absolute irresponsive period (msec.)*
1	10	2.3±0.1	3.2±0.1
4	10	2.9±0.2	3.8±0.1
5	8	3.7±0.3	4.5±0.2

Severely dystrophic muscles (force graded as 0 to 3) and slightly dystrophic muscles or muscles with normal force (graded as 4 to 5) showed identical absolute refractory periods—2.5 ± 0.1 msec. in 22 and 16 muscle fiber bundles. The absolute irresponsive periods in severely paretic muscles were 15% longer than in slightly paretic muscles or in muscles with normal force (3.6 ± 0.1 msec.).

Of the 38 determinations of absolute refractory and irresponsive periods, 20 fiber bundles were studied in muscles from patients with the pseudohypertrophic type of the disease and 16 bundles from patients with the facioscapulohumeral or limb-girdle type. The absolute refractory periods were the same in

the 3 groups (2.5 ± 0.1 msec.). The absolute irresponsive period in the pseudohypertrophic type was 15% longer than in the other types, because of the more advanced degree of paresis in these patients (3.7 ± 0.1 msec. as compared with 3.2 ± 0.1 msec.).

Peripheral nerve injury. In all, 20 fiber bundles were investigated in paresis due to damage of peripheral nerve. The absolute refractory period averaged 5.3 ± 0.4 msec., 50% longer than the average of normal muscle (3.6 ± 0.1 msec.; repetition rate of paired stimuli, 1 per second). In 10 bundles, the absolute refractory period was prolonged (5 to 8 msec.) and, in 10, ranged as in normals, between 2.6 and 4.8 msec. Both types of bundles were found in the same muscle; in only 1 patient did all fibers tested have normal refractory and irresponsive periods. In this muscle, fibrillation potentials were absent.

A prolonged absolute refractory period was observed as early as seventeen days after the nerve injury, before fibrillation potentials had developed. On the other hand, fiber bundles with absolute refractory periods within the normal range occurred in a muscle in which the motor innervation had been entirely interrupted for seven months.

The examples given in Figure 5 were recorded in a femoral rectus muscle in which motor innervation was completely interrupted. The strength of the testing stimulus could be increased to 2.6 times threshold without interference from the action potentials of neighboring fibers. The absolute refractory period was prolonged to 6.8 msec. in Figure 5*A* and at the upper limit of the normal range (4.8 msec.) in Figure 5*B*. As in normal muscle, the absolute irresponsive and refractory periods were the same within 0.4 msec. In Figure 5*C*, the refractory and irresponsive periods are plotted against the strength of the testing stimulus for the action potentials that are shown in *A* and *B*.

As in normal muscle, the absolute refractory and irresponsive periods increased with increasing repeat rate of the paired stimuli. The increase was 30% between 1 and 4 paired stimuli per second (9 fiber bundles) and 90% between 1 and 5 stimuli per second (5 bundles). In fibers with a prolonged refractory period, there was also evidence of a supernormal period 8 to 30 msec. after the conditioning action potential.

The total duration of the action potentials evoked by electrical stimuli was 35% longer in the paretic than in the normal muscles (4.8 ± 0.3 msec., 21 different action potentials, as compared with 3.5 ± 0.2 msec., 31 action potentials in normal muscle).

Anterior horn cell involvement. The refractory and irresponsive periods in 23 muscle fiber bundles from 4 patients with advanced amyotrophic lateral sclerosis were within the limits of normal muscle. The absolute refractory period averaged 3.4 ± 0.1 msec., as compared with 3.6 ± 0.1 msec. in normal muscle, and was distributed in the same 2 groups found in normal muscles.[1] The absolute irresponsive period averaged 3.7 ± 0.1 msec. in both paretic and normal muscle fiber bundles.

In a patient with peroneal muscular atrophy (10 muscle fiber bundles) and in a patient with infantile progressive spinal atrophy (6 bundles), the absolute refractory period ranged from 2.2 to 3.2 msec., corresponding to the group with short refractory periods in normal muscle. In the patient with infantile spinal atrophy, the absolute irresponsive period exceeded the absolute refractory by more than 1 msec.

In patients with anterior horn cell involvement, the increase in refractory period with increasing repeat rate of paired stimuli, the reduction in voltage of the second action potential, and the occurrence of a supernormal phase were as in normal muscle.

DISCUSSION

There are several lines of evidence that the muscle fiber membrane is altered in neuropathy and advanced cases of myopathy: the occurrence of spontaneous discharges from muscle fibers; the increase in excitability to mechanical stimuli (insertional activity); and the changes in strength-duration curves. It was therefore of interest to investigate whether the change in the muscle fiber membrane might also change recovery of excitability after passage of a propagated action potential.

In dystrophic muscle, the refractory period of directly activated small fiber bundles was shorter than that of normal muscle. The decrease of the refractory period is consistent with the decrease in intracellular potassium

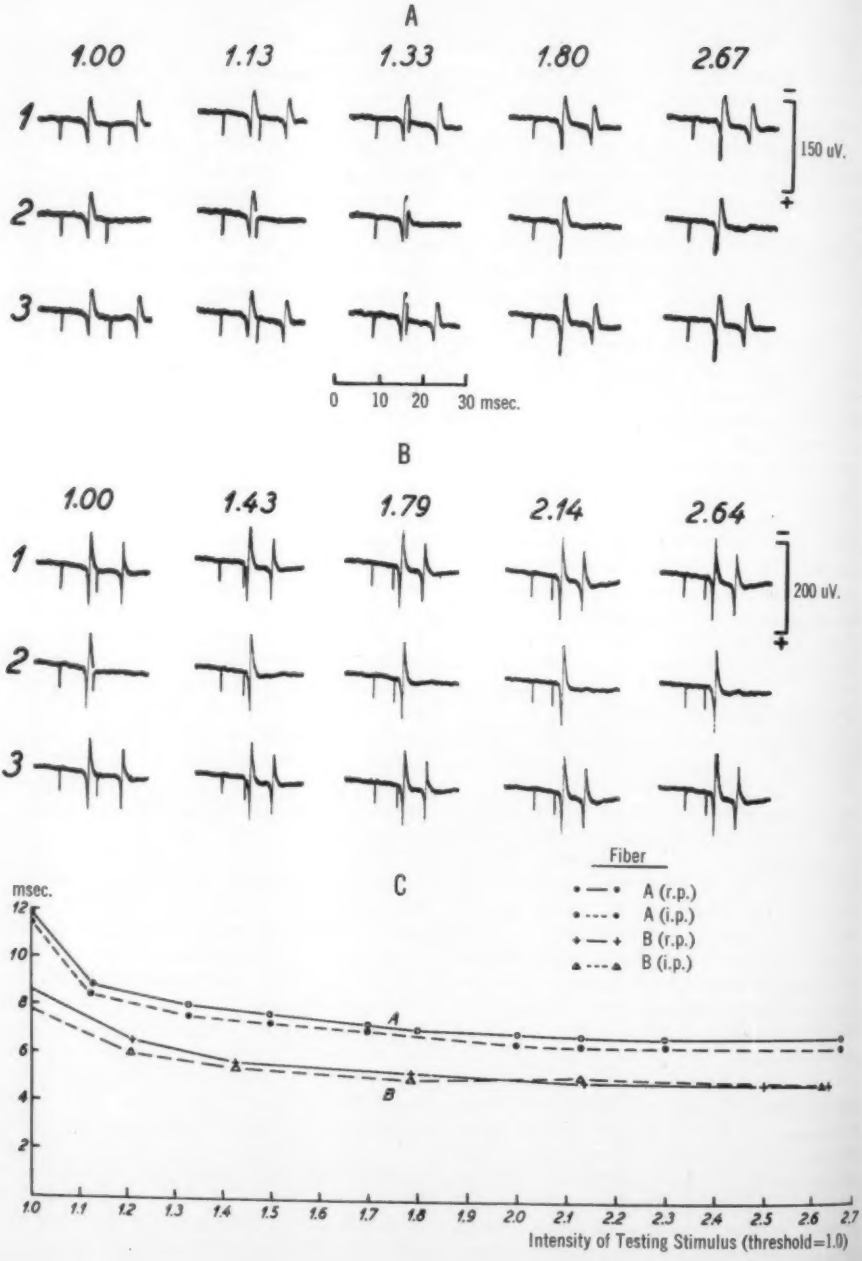
A
1.00
1.13
1.33
1.80
2.67
1
2
3
150 uV.
0 10 20 30 msec.
B
1.00
1.43
1.79
2.14
2.64
1
2
3
200 uV.
C
msec.
Fiber
A (r.p.)
A (i.p.)
B (r.p.)
B (i.p.)
12
10
8
6
4
2
A
B
1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0 2.1 2.2 2.3 2.4 2.5 2.6 2.7
Intensity of Testing Stimulus (threshold=1.0)

Fig. 5. Illustrating action potentials from muscle fiber bundles of the femoral rectus muscle with clearly increased [A] and slightly increased [B] refractory periods in peripheral nerve injury. Damage to the femoral nerve one month ago. The figure above each column denotes strength of testing stimulus. The stimulus is indicated by the vertical positive deflection. In some cases in *A* the second stimulus mark coincides with the first action potential. Frequency of paired stimuli, 1 per second; intramuscular temperature, 36.6° C. [C] Refractory and irresponsive periods of fiber bundles *A* and *B* are plotted as functions of the strength of the testing stimulus.

to an average of half that in normal muscle,[4] causing a reduction in the potential across the muscle fiber membrane of about 15 mv. and, hence, an increase in excitability. Diminished potassium values were also found in subclinical or minimal muscular dystrophy cases,[5] and, in this connection, it is of special interest that a shortened refractory period was observed in the muscles of patients with progressive muscular dystrophy, which showed no or only slight reduction in force.

The reduction in the refractory period in dystrophic muscle was due to an over-all reduction in this condition; 40% of the dystrophic fibers had refractory periods shorter than ever seen in normal muscle, whereas the absolute irresponsive periods were distributed over the same range as those in normal muscle, indicating that there was no selective loss of those fibers with long refractory period.

That the reduction of absolute refractory period was not attributable to a selective activation of hypertrophic fibers is indicated by the finding of the same short refractory period in muscles that, on biopsy, showed only very few hypertrophic fibers and in muscles with a high incidence of hypertrophic fibers (diameter measurements on biopsies in 9 of the 11 patients with dystrophy). The characteristics of the stimulating field made it unlikely that especially excitable fibers were selected by this method.[2]

The absolute irresponsive periods of dystrophic muscle were up to 2.5 msec. longer than the absolute refractory periods, a much greater delay than in normal muscle. Such an increased latency of the second action potential can be due to either a diminished conduction velocity or a delayed firing of the propagated response due to a prolongation of the local response that precedes the rapid depolarization at the point of stimulation. Preliminary measurements indicate the conduction velocity of a potential evoked by a single stimulus to be normal in dystrophic muscle. In normal human muscle, delayed firing caused the irresponsive periods to exceed the refractory periods.[1] The great variability of the absolute irresponsive periods at a given absolute refractory period (Fig. 4) suggests that, in dystrophic muscle too, delayed firing of the second action potential is mainly responsible for the longer irresponsive period. In frog muscle fibers, both factors, prolonged conduction time and delayed firing, were responsible for the longer irresponsive period.[6]

The high degree of variability of the absolute irresponsive periods reflects the instability of the muscle fiber membrane, when the local response is superseded by the propagated action potential. A similar prolonged local response has frequently been observed in frog muscle when the resting membrane potential of the muscle fibers was reduced.[6]

The failure of Glaser and Stark[7] to find the pronounced reduction in refractory period reported here is presumably due to the method used. They activate many fibers by a conditioning stimulus and deduce the recovery of excitability from the voltage of the action potential evoked by the testing stimulus at different time intervals. In our experiments, all-or-none responses were evoked by activating small fiber bundles directly. The amplitude of the action potential evoked by the testing stimulus did not diminish appreciably with decreasing time interval between stimuli, being lower than the conditioning action potential by no more than 15% near the absolute refractory period. Therefore, in Glaser and Stark's procedure, the diminished voltage of the second action potential is due to the responding of fewer muscle fibers rather than to a reduced response amplitude of individual fibers. The refractory periods obtained in this way are attributable to the fibers with shortest refractory periods; fiber groups with long refractory periods in normal muscle are concealed. Hence, the difference between normal and dystrophic muscle is not apparent.

In the majority of small fiber bundles investigated in paresis secondary to peripheral nerve injury, the refractory periods were longer than those in normal muscle. Even refractory periods within the normal range might, in fact, have been prolonged, since no values below 2.8 msec. were observed. The prolongation of the refractory period cannot be explained in terms of an increase in intracellular potassium, since the concentration of this ion per gram muscle weight does not vary significantly with denervation.[8] Neither can a decrease in excitability account for it; on the contrary, there is, in denervated muscle, a substantial decrease in threshold both to extracellularly and intracellularly applied stimuli.[9]

There are, on the other hand, changes in denervated muscle which can explain the prolongation of the refractory period. The rate of repolarization of muscle fibers, measured intracellularly in rat diaphragm, falls to less than half within two to three weeks after denervation,[10] implying an increase in the refractory period. The delayed repolarization has been attributed to changes in the electrical properties of the muscle fiber membrane. Such changes are also indicated by the reduced conduction velocity[11] and by the prolonged duration of electrically evoked potentials in denervated human muscle (cf. p. 7).

The absence of a prolonged refractory period in paresis secondary to anterior horn cell involvement was probably due to the relatively larger number of intact fibers in these muscles, their average force being graded as 2+ as compared with 1 in paresis due to peripheral nerve lesions.

SUMMARY

The course of recovery was determined after the passage of a propagated action potential in directly stimulated small fiber bundles in muscles of patients with progressive muscular dystrophy and with paresis due to lower motor neuron involvement.

In *dystrophic muscle*, the absolute refractory period averaged 2.5 ± 0.1 msec. as compared with 3.6 ± 0.1 msec. in normal muscle. This decrease was due to an over-all reduction in refractory period rather than to a selective loss of the fibers with long refractory periods found in normal muscle. The reduction in refractory period was found even in muscles with no or only a minimal force reduction and had the same degree in the pseudohypertrophic and facioscapulohumeral or limb-girdle types of the disease. It can be explained by the decrease in intracellular potassium and the resulting increase in excitability.

The absolute irresponsive periods of dystrophic muscle did not deviate from those of normal muscle and exceeded the absolute refractory period by, on the average, 1 msec. as compared with 0.1 msec. in normal muscle.

In paresis due to *peripheral nerve injury*, the absolute refractory period was 50% longer than in normal muscle. This can be explained by the changes in membrane properties caused by denervation and evidenced by the slower rate of repolarization[10] and the reduced conduction velocity.[11] Difference between refractory and irresponsive periods was slight.

In paresis secondary to *anterior horn cell involvement*, the absolute refractory and irresponsive periods were within the limits of normal muscle. This was probably due to the relatively larger number of intact muscle fibers in these muscles (average force graded as 2+) as compared with paresis in peripheral nerve injury (average force graded as 1).

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Incidence and type of pathologic alterations observed in muscle in a routine autopsy survey

Carl M. Pearson, M.D.

MUSCLE BIOPSY is a common diagnostic procedure used in the work-up of persons with various forms of muscular or neuromuscular disease, as well as in a number of ill defined systemic disorders or in persons with fever of obscure origin. In the former groups, a reasonable approximation of the nature of the neurologic disease can be made in many of the cases, provided that the site for muscle biopsy is carefully selected. In the latter group, however, rarely does one discover a specific feature that would allow further clarification of the perplexing underlying disease process. If degenerative changes are observed in the muscle fibers or interstitial or perivascular inflammatory infiltrates are found, these are considered to be "consistent with the disease under consideration," which is often one of the connective tissue or collagen disorders.

It has not been generally appreciated that a number of similar or identical changes may occur in a wide variety of chronic disease states that are unrelated to the collagen diseases. Many years ago, Zenker[23] pointed out that a characteristic hyalinizing change may affect the sarcoplasmic constituents of the muscle fibers in many cases of typhoid fever. This change has since been known as Zenker's degeneration. Identical changes have been noted in a variety of infectious diseases, and the rectus abdominis has been the muscle most commonly affected, although a detailed survey of the body musculature has not been undertaken. These various diseases include epidemic influenza,[22] pneumonia,[7,8] small pox, paratyphoid fever, infectious hepatitis, Weil's disease (leptospirosis), and others. In all of these conditions, the myopathy is thought to be caused by a circulating toxin liberated by the infectious agent. Organisms have not been found in the muscle lesions, with the single recent exception that Sheldon[16] has demonstrated leptospiral antigen (presumably the organisms) in the vicinity of necrotic muscle lesions in Weil's disease with the aid of the fluorescent-labeled antibody technic.

Myositis, or inflammatory infiltrates in muscle, are always found in direct bacterial infections and most parasitic invasions of muscle. They are also present, but in variable degrees, in dermatomyositis and polymyositis.[13,20] In recent years, it has been recognized that focal interstitial or perivascular collections of chronic inflammatory cells are commonly present in all of the collagen diseases, especially rheumatoid arthritis.[1] Furthermore, focal interstitial infiltrates of small lymphocytes, so-called lymphorrhages, are frequently seen in myasthenia gravis. As will be pointed out, focal myositis may occur in a variety of disease states other than the collagen diseases, but, in our material, it is not as common as degeneration.

Most of the myopathic or neuromuscular disorders can only be strongly suspected by their histologic appearance, and there are only a few specific entities that can be diagnosed with certainty from the muscle biopsy. These include polyarteritis, sarcoidosis,[9,18] amyloidosis, tuberculosis, trichinosis, toxoplasmosis and certain other parasitic infestations, and metastatic malignancy.

This survey of the histopathology of a series of muscles in routine autopsy material

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TABLE 1
MUSCLES ROUTINELY EXAMINED FROM 110 AUTOPSIES; INCIDENCE OF PATHOLOGIC CHANGE

Muscle	*Number examined*	*Number affected*
Quadriceps femoris	105	21
Iliopsoas	110	26
Rectus abdominis	110	31
Diaphragm	110	48
Intercostal	107	12
Pectoral	107	20
Deltoid	110	30
Sternocleidomastoid	104	22
Extraocular	67	3
	930	213

was prompted by the finding of a significant number of isolated degenerative and regenerative changes in many muscles of several persons that died of malignancy.

METHODS OF SELECTION AND EXAMINATION OF CASES

In all, 930 muscles from 110 autopsies were examined histologically; the distribution of sections from predetermined sites are enumerated in Table 1. Most of the cases were embalmed soon after death, and hence many muscles were partially fixed before gross dissection. Muscle tissues were aligned on cardboard and fixed in 10% neutral formalin. After routine paraffin embedding, all were cut longitudinally and transversely and sections were stained with hematoxylin and eosin. A few sections, as indicated later, were stained with azure B bromide at *p*H 4 to demonstrate ribonucleic acid (RNA).

INCIDENCE OF PATHOLOGIC CHANGE

There was an overwhelming preponderance of males, 107 in number, in the series. All decades through the tenth were represented, with the majority of the cases occurring in the sixth and seventh decades (Table 2). In 54 of the 110 cases (49%), some type of abnormality was observed in the muscle fibers or the adjacent structures of one or more muscles. Furthermore, 213 of the 930 muscles examined (23%) showed some minor or major alteration, and the diaphragm, rectus abdominis, and deltoid were the muscles most frequently affected. As demonstrated in Tables 1 and 2, alterations occured at almost any age and in any muscle in the presence of serious disease.

TYPE AND DISTRIBUTION OF PATHOLOGIC CHANGE

The histologic alterations varied widely in form as well as in intensity. In a few cases, focal lesions involved an occasional fiber in only 1 muscle; in many, moderate alterations were found in 2 or more muscles; and, in several, there were widely dispersed changes in many muscles. In Table 3 are enumerated the types of lesions found, the number of cases in which each type of lesion was observed, and the total number of muscles afflicted with each type of change. Degenerative and regenerative changes in muscle fibers were observed most commonly. They were not diagnostic of any particular condition, but their presence suggested a debilitating disease. Likewise, interstitial or perivascular inflammatory foci were nonspecific except for 1 case of necrosing arteritis, which was typical of polyarteritis nodosa.

In addition, certain other nonspecific alterations were observed in about one-third of the cases, especially in advanced malignancy or comparably serious chronic disease. These changes, usually called simple atrophy, were the results of malnutrition, inactivity, or emaciation caused by the underlying debilitating disease state. Histologically, they consisted of

TABLE 2
AGE DISTRIBUTION AND INCIDENCE OF PATHOLOGIC CHANGE IN MUSCLES FROM 110 AUTOPSIED CASES

Age	*Number of cases*	*Number with pathology in muscle*	*Per cent with pathology at various ages*
0 to 9	2	0	0
10 to 19	1	0	0
20 to 29	1	1	100
30 to 39	7	4	57
40 to 49	7	2	29
50 to 59	21	11	52
60 to 69	54	31	57
70 to 79	13	5	38
80 to 89	3	0	0
90 to 99	1	0	0
	110	54	49

107 males, 3 females; 101 Caucasian, 7 Negro, 1 American Indian, 1 Oriental

a variable reduction in the volume of fibers and a striking increase in the number of inactive-appearing sarcolemmic nuclei. These alterations have not been tabulated in the overall survey of the pathologic changes observed in the present series because they are of little importance in the final evaluation of myopathic disease.

The specific lesions observed in this series were blood-borne metastatic tumor nodules in 14 muscles in 6 of 38 cases of malignancy and incidental ancient trichina parasites in 14 muscles in 5 cases. Denervation atrophy was present in 1 muscle in each of 3 cases (polyarteritis, prostatic carcinoma, and rheumatoid arthritis). There were no diagnostic granulomas or evidence of amyloidosis in this series.

Degeneration. Degenerative changes were observed in muscle fibers in 38 cases, nearly one-third of those studied, and were present in several muscles in many of the cases, so that, in all, 85 muscles were involved (Table 3). The diaphragm was affected most commonly, in 21 cases, the rectus abdominis in 14, the deltoid in 12, and others with lesser frequency, down to an extraocular muscle that was affected once. The degenerative alterations could be divided into 3 forms: (a) hyaline or waxy (Zenker's) degeneration, (b) granular degeneration, and (c) vacuolar degeneration. Often 2 or all 3 forms were present in a single muscle, so that none was specific for a particular disease state. Hyaline degeneration was most frequently encountered and consisted of contraction and swelling of one or more segments of a fiber, with complete disappearance of the cross and longitudinal striae (Fig. 1). Frequently, the necrotic segments were invaded and phagocytosed by macrophages and other mononuclears (Fig. 2). Regenerative activities were often prominent at the junction of the necrotic and healthy segments of the fibers. Granular degeneration was much less common. In this condition, larger segments of a muscle fiber were swollen, granular, and opaque with complete disappearance of all striations. Vacuolar degeneration was the mildest change. It consisted of multiple, clear, watery vacuoles, often centrally placed (Fig. 3) and longitudinally compressed between myofibrils.

Regeneration. Features indicative of regen-

TABLE 3

TYPE AND INCIDENCE OF PATHOLOGIC CHANGES IN SECTIONS OF 930 MUSCLES

Type of alteration	*Number of cases involved*	*Total number of muscles affected*
Degeneration of muscle fibers	38	85
Regenerative features	25	54
Focal interstitial myositis	7	8
Perivascular mononuclear cell foci	13	35
Trichina parasites	5	14
Metastatic tumor	6	14
Focal denervation atrophy	3	3
		213

Fig. 1. Zenker's hyaline degeneration in an isolated segment of 1 muscle fiber from the sternocleidomastoid muscle of a 63-year-old male who died with a squamous cell carcinoma of the tonsil without metastases. There were many degenerative and some regenerative changes in this muscle and the deltoid. The transverse cracks are artifactually induced by the section knife. Hematoxylin and eosin. × 645

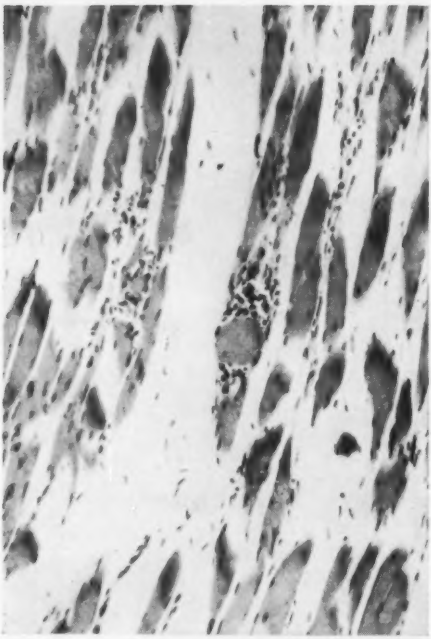

Fig. 2. Hyalinization and phagocytosis in 2 muscle fibers in the rectus abdominis of a 61-year-old man who died with chronic nephritis and uremia. Hematoxylin and eosin. × 210

erative repair of previously damaged muscle were found in 54 muscles in 25 cases. They were always associated with some obvious or resolving evidence of degeneration. Again, the diaphragm was affected most commonly, in 16 instances, the deltoid in 9, and the rectus abdominis in 8. All other muscles except the extraocular showed a few regenerating fibers.

The 2 most reliable criteria for evidence of regeneration in the present material have been the appearance of basophilia in fibers by the hematoxylin and eosin stain and the proliferation of large, plump sarcolemmal nuclei, most of which contain 1 or 2 prominent nucleoli. The presence of one or several muscle buds, sprouting from healthy muscle into a previously damaged area or bridging a gap to the opposite uninjured segment of the fiber, is conclusive evidence for this process. A regenerating fiber is illustrated in Figure 4. The phenomena of basophilia were further examined with the stain azure B bromide. At *p*H 4, this dye stains ribonucleic acid a purple color, while other acidic substances are a pale blue or colorless. The significance of RNA in the interpretation of regeneration lies in the fact that its presence usually indicates active protein synthesis and hence, indirectly, reparative processes in the muscle fibers. Fibers that take a basophilic stain by routine methods invariably disclose the presence of significant quantities of RNA by this method (Fig. 5).

Focal interstitial myositis. Focal infiltrates of inflammatory cells were found in 8 muscles in a total of 7 cases. They consisted of small loose collections of uniform dark cells resembling adult lymphocytes, which were distributed between and about muscle fibers in

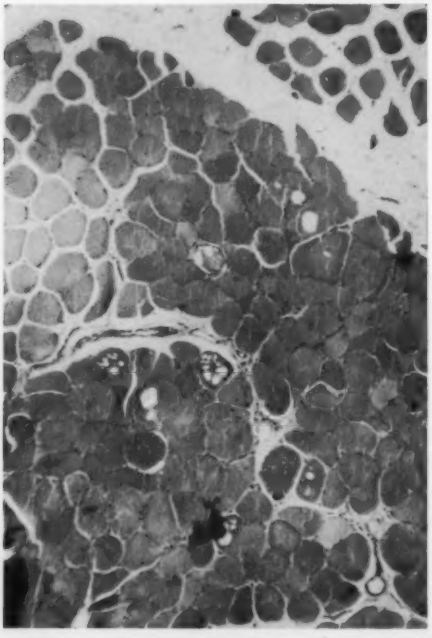

Fig. 3. Focal vacuolization in several fibers of the deltoid of a 63-year-old man who died of decompensated portal cirrhosis. Similar vacuoles were observed in many muscles and other degenerative changes were present in some. Hematoxylin and eosin. × 175

Fig. 4. Regeneration of 1 muscle fiber (dark segment) in the sternocleidomastoid muscle of a 63-year-old man who died twelve days after an acute myocardial infarction. The dark fiber stained deeply basophilic. Note the multiple sarcolemmic nuclei in it and the number of plump nuclei in the broad fiber directly above. Some repair has likely just been completed in this fiber. Hematoxylin and eosin. × 150

the endomysial and, occasionally, the perimysial connective tissues. They were found in a variety of unrelated conditions (Table 4) and only in the single case of myasthenia gravis, in which they were seen in 2 muscles (as lymphorrhages), did they have any possible significance.

Perivascular inflammatory foci. Mononuclear collections of inflammatory cells about the adventitia of small intramuscular veins or arteries were found during 12 autopsies. In another case, the arteries were involved in a necrosing process with acute and chronic cell invasion of all layers, which was typical of polyarteritis. Hence, in all, 35 muscles revealed vasculitis in a total of 13 cases, and this change was seen in a wide variety of clinical disease states (Table 4). The perivascular collections of cells consisted largely of adult lymphocytes, but other cells, including plasma cells and histiocytes, were also encountered (Fig. 6). In addition to an extensive perivasculitis, diffuse infiltrates of mononuclear cells between muscle fibers and quite extensive degenerative and regenerative features were found in 2 cases of advanced chronic rheumatoid arthritis (Fig. 7). Many muscles were affected in this process, and, in some respects, the histopathology in these cases could not be differentiated from that seen in polymyositis or dermatomyositis.[13,20]

Trichinosis. Incidental trichina parasites were

Fig. 5. A solitary regenerating fiber, as demonstrated by a specific stain for ribonucleic acid. Note the intense staining of the nucleoli and the nuclear membranes and the coloration of the newly formed sarcoplasm in contrast to the absence of staining of the mature adjacent fibers. Biopsy is from the iliopsoas of a 68-year-old man who died of lobar pneumonia. Azure B bromide, *p*H 4. × 645

TABLE 4
MAJOR DISEASE AND PATHOLOGIC ALTERATION IN MUSCLE

Diagnosis	Number of cases	Number showing: Degeneration and regeneration	Interstitial myositis	Perivascular cellular foci
Malignancy	38	12	1	2
Congestive heart failure	9	4	2	1
Myocardial infarction	9	2	0	1
Hypertension	4	1	0	0
Cerebral vascular disease	9	2	0	0
Acute hemorrhage (ulcer; aorta)	4	2	0	0
Rheumatoid arthritis	6	5	2	2
Polyarteritis	1	0	0	1
Lupus erythematosus	1	1	0	1
Cirrhosis, decompensated	5	3	0	0
Diabetes mellitus	2	0	0	1
Pyelonephritis	2	0	0	0
Septicemia	1	1	1	1
Bronchopneumonia	3	2	0	1
Cor pulmonale	1	1	0	0
Uremia	2	1	0	0
Duodenal ulcer	2	1	0	1
Severe trauma	2	1	0	0
Myasthenia gravis	1	1	1	1
Miscellaneous conditions	8			
	110	40	7	13

found in 5 cases. In each, they appeared to have been present for some time, and, in several, most of the encysted larvae were partially or completely removed (Fig. 8). Interestingly enough, the diaphragm, usually said to be the commonest site of invasion, was affected only once, whereas the iliopsoas was involved in all 5 cases.

Metastatic malignancy. Metastatic tumorous growths were found in 14 muscles in 6 cases from a total of 38 that harbored malignancy at the time of death. This is somewhat in contrast to the usual statement[21] that tumor rarely disseminates into muscle despite undoubted numerous opportunities to do so. Direct invasion of muscle from an adjacent organ such as the breast was not considered in this analysis. The iliopsoas contained tumor 4 times, the diaphragm thrice, and all others except the pectoral at least once; 3 of the tumors were lymphomas (reticulum cell sarcoma, myelogenous leukemia, and giant follicle lymphoma with sarcomatous change). The carcinomas originated in the ampulla of Vater, stomach, and male breast. Each of the tumors had spread to remote muscles as tumor emboli or as perimysial growths (Fig. 9) adjacent to a blood vessel. The metastatic growth oftentimes destroyed adjacent muscle fibers by direct invasion. None of the metastases was recognizable grossly. Each of the carcinomas retained its acinar or scirrhous growth pattern as seen in the primary tumor.

CORRELATION BETWEEN CLINICAL DISEASE AND MUSCLE LESIONS

Tabulated in Table 4 is a list of the various major disease states and the type of alteration found in the muscles. As expected, the several systemic connective tissue diseases (rheumatoid arthritis, lupus erythematosus, and polyarteritis) showed change in the muscle fibers or perivascular tissues in a significant proportion of cases (100% in this series). Of greater interest was the finding of degenerative or inflammatory lesions in single or multiple muscle sections from a wide variety of disease states. Of 38 cases with malignancy, 12 showed degen-

Fig. 6. Perivascular infiltration of a perineural artery in the quadriceps femoris of a 61-year-old man who died with advanced metastatic carcinoma of the prostate. Hematoxylin and eosin. × 150

erative and regenerative changes and a rare inflammatory infiltrate. In 13 cases of pulmonary malignancy, 5 had abnormalities. Of the 4 cases of carcinoma of the oral cavity, 3 also showed degenerative changes. A wide variety of systemic and serious local medical disorders, as shown in Table 4, demonstrated an array of muscle alterations, occasionally quite impressive, in the absence of apparent clinical muscular symptomatology.

DISCUSSION

The results of this study are of basic importance in the diagnostic interpretation of muscle biopsy material and provide insight into the distribution and methods by which skeletal muscle reacts to a variety of serious disease states. Since histologic alterations have been observed in a considerable proportion of these cases, caution should be exercised in the interpretation of focal changes in the muscle fiber substance or the interstitium, and, at our present state of knowledge, clinical correlation, especially with reference to the status of the musculature, should be considered before a specific diagnosis of myositis or other disease entity is offered.

The incidence of alterations has only once been reported to be as high as that described in this series. Clawson and associates[2] examined 7 muscles from each of 450 autopsies and observed an over-all occurrence of at least 1 type of lesion in 65.1% of their series. However, they included in their evaluation evidence of simple atrophy but excluded regenerative features. Their sizable series merits careful consideration. In an analysis of nonrheumatic diseases, they noted muscle lesions in 39.1% of 46 malignant tumors, 55% of 9 cases

Fig. 7. Diffuse interstitial myositis with focal destruction and phagocytosis of several fibers. Biopsy is from the diaphragm of a 62-year-old man who died with advanced rheumatoid arthritis and hepatic cirrhosis. Hematoxylin and eosin. × 75

Fig. 8. An ancient trichina parasite in the iliopsoas muscle of a 61-year-old man who died with congestive heart failure. Note the thick homogenous capsule, the scant surrounding cellular reaction, and the almost complete dissolution of the encapsulated parasite. Hematoxylin and eosin. × 150

of cirrhosis, and 25.5% of 43 persons dying from accident or trauma. They noted no difference between male and female patients in the occurrence of lesions, a point we were unable to resolve because of the great preponderance of males in our series. The frequency with which lesions are encountered seems to be a function of the number of muscles examined as well the selection of clinical case material. Most other series record a lesser incidence of alterations, but these are usually based on one or a few biopsies in each case. Wallace and associates[19] noted pathology in 12 of 76 cases (16%) by surgical biopsy, exclusive of cases with connective tissue disease. Cruickshank,[3] who uses the term lymphorrhage to include all forms of inflammatory cell infiltrate in muscle including interstitial and perivascular collections, observed such foci in 8% of 419 nonrheumatic cases and 48% of 166 "rheumatic" cases. He found degenerative alterations in only 10% of 244 muscles studied. Sokoloff and associates,[17] on the other hand, noted some change in 25% of biopsies from 145 persons with various disease states other than rheumatoid arthritis, and this compares closely with our finding of alterations in 23% of the 930 individual muscles sampled in the present series.

The 2 disorders most commonly associated with lesions, both inflammatory and degenerative, are myasthenia gravis[14,15] and one of the connective tissue disorders, especially rheumatoid arthritis.[1–3,17] The few persons in our series who died with these diseases had a high incidence of various lesions in their muscles (Table 4).

Features of regeneration of muscle fibers have been largely overlooked in all of the previous series or have only been mentioned

Fig. 9. A metastatic nodule of anaplastic carcinoma in the perimysium in an iliopsoas muscle in a 63-year-old man. The primary tumor arose in the ampulla of Vater. Hematoxylin and eosin. × 150

casually in a few. They are somewhat difficult to recognize in routine stains, and the mild or moderate basophilia of the reparative process, plus the presence of "activated" sarcolemmic nuclei in a segment of a fiber, can be detected only after some practice. The azure B bromide method of staining for RNA allows us to be much more certain of the presence of this response than does the routine hematoxylin and eosin stain, which is rather crude and oftentimes fails to reveal minor degrees of damage and subsequent repair to muscle fibers. With the azure method, it was often possible to detect evidence of repair of a much more subtle order than could be seen by other methods.

It appears from these observations that muscle tissue is continuously undergoing some degeneration and repair in many disease states and perhaps even in the healthy individual. From experimental studies in animals,[12] we have observed that muscle fibers may completely and functionally be repaired in 12 days or less following total necrosis of segments. Since destructive and regenerative processes definitely occur in a wide variety of disease states, it is possible that an excess of the former in comparison to the latter may contribute significantly to the muscular weakness and wasting of the chronic disease state.

Why and how do such changes as degeneration and regeneration occur in muscle fibers in such a wide variety of diseases? The explanations are very likely multiple since muscle tissue has a limited pattern by which it can respond to a variety of noxious agents. In some cases, hypoxia, electrolyte disturbances, infection, or "toxemia" are very likely responsible. Furthermore, it should be recalled that, in addition to its primary function of contractility, muscle also serves as a source of available body protein and, under many stressful situations, rapid protein withdrawal may induce necrosis in some fibers as well as a general reduction in bulk of most of them. This process very likely accounts for the degenerative changes found in muscle in the presence of malignant disease and occasionally seen in extreme degree in cases such as the 2 reported by Denny-Brown[5] or some of those reported by Henson and associates[11] and Heatherfield and Williams[10] in association with bronchogenic carcinoma. It is interesting to speculate about the relationship between these focal degenerative changes and the well recognized association between dermatomyositis and visceral malignancy.[4,6]

Only 3 specific entities were recognized in a few muscles in this series. They were trichinosis, metastatic malignancy, and necrosing arteritis typical of polyarteritis nodosa. In the group of 5 cases that had trichina parasites in muscle, it was of interest to note that the iliopsoas group was involved in each case, whereas the diaphragm, which is traditionally the muscle most often affected, contained parasites only once and the extraocular muscles not at all. The incidence of 16% metastases of tumor to muscle is a much higher figure than has been previously reported. Willis[21] observed muscle metastases in only 4 cases in a report on the study of 500 consecutive cancer necropsies, a frequency of only 0.8%. However, he very likely sampled only 1 or 2 muscles, and, as has been seen in this series, the likelihood of finding any type of pathology, including metastases, increases almost in proportion to the number of muscles (or portions of a single muscle) examined.

None of the histologic changes observed in muscle, except those listed directly above, can be considered to be specific for any particular disease process. They are found most commonly in certain conditions, such as myasthenia gravis or one of the connective tissue disorders, but may also occur in a wide variety of infectious and noninfectious disease states. It is likely that they are intimately concerned with the muscular weakness and wasting that are frequently prominent features of the chronic disease state. In addition, their importance lies in the recognition that a single muscle biopsy, even if it shows several pathologic lesions, is almost valueless in the diagnosis of a specific clinical disease entity.

SUMMARY

Multiple muscle biopsies were taken at autopsy from 9 predetermined sites in 110 routine autopsies. Careful histologic study of this material has disclosed that, in 54 cases, or 49%, some type of abnormality was observed in the muscle fibers or the adjacent

structures of one or more muscles. The nonspecific alterations observed included various types of degeneration and regeneration of muscle fibers as well as interstitial or perivascular inflammatory infiltrates. These were found most commonly in one of the connective tissue disorders or in myasthenia gravis but were seen in a wide variety of unrelated disease states.

Specific lesions observed in this series included trichina parasites in 5 cases and metastatic tumor nodules in 16% of 38 cases with malignancy.

The interpretation of regeneration of muscle has been discussed in some detail, and this phenomenon has been studied by special methods.

It was pointed out that the observed nonspecific lesions most likely contribute to the general loss of muscular strength and debility in the chronic disease state and that none of them can be relied upon to specifically clarify the clinical diagnosis of the disease under consideration.

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The clinical syndrome of paroxysmal paralytic myoglobinuria

Report of 2 cases and an analytical review of the literature

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IDIOPATHIC or paroxysmal paralytic myoglobinuria is a rare syndrome first described in man by Meyer-Betz in 1910.[1] Myoglobin is a respiratory pigment of striated muscle and is normally not present in the urine. However, myoglobinuria is associated with Haff disease,[2] the crush syndrome,[3] massive infarction of striated muscle,[4] and, occasionally, high voltage electric shock.[5] In these conditions, there are apparent disruption of the sarcoplasm and destructive changes in the sarcolemmic sheath, which may be directly related to the noxious agents involved. Myoglobin is then released into the circulation and passes through the kidneys into the urine. The urine turns dark red-brown and exhibits positive tests for protein and blood, although no erythrocytes are present. The pigment, myoglobin, can be identified absolutely by spectroscopic examination.

Myoglobinuria of unknown cause may be a primary disturbance of striated muscle and has been compared to equine paralytic myoglobinemia, which is relatively common in work horses. Since the original description of the disease in man, over 40 cases have been reported in the literature. In the present review, the authors present 2 additional cases they have diagnosed and studied. An attempt is made to correlate these cases and those previously described into clinically distinct groups and discuss the possible pathophysiology and etiologies involved.

CASE REPORTS

Case 1. A 52-year-old white male was admitted to Tripler Army Hospital because painful muscles made him unable to work. The patient's muscular difficulty began at 18 years of age, when he first noted muscular cramps and pain in the calves of his legs following a march. Before that time, he had participated in strenuous exercise without ill effect. Following this first episode, he noted that, after heavy physical activity, almost any muscle would become painful and tender and go into "spasm." The muscle cramps usually lasted about eight to twelve hours, and the pain subsided after twelve to forty-eight hours. Muscular swelling was noted most often in the anterior muscles of the thigh but also occurred in the calves, trunk, and upper extremities. At the age of 22, in addition to the above symptoms, he had his first episode of voiding dark red urine, which persisted for a period of eight to twelve hours. Since then, he has on many occasions voided dark red urine two to four hours after sustained muscular effort. He has been able to perform light muscular work without causing symptoms, provided no sustained effort was required. Family history was noncontributory. There were no siblings and no history of similar difficulty among known relatives.

Physical examination revealed a well developed, moderately obese male weighing 196 lb. Blood pressure was 160/90. The remainder of the physical and neurologic examination was within normal limits. Muscle mass and tone appeared to be normal, and no muscular weakness was observed.

Admission hemogram, erythrocyte sedimentation rate, serology, urinalysis, electrocardiogram, and chest roentgenogram were within normal limits. An oral glucose tolerance test revealed a diabetic-type curve.

The patient was subjected to an exercise test to precipitate an attack, so that the clinical phe-

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TABLE 1
SIGNIFICANT LABORATORY FINDINGS—CASE 1

Laboratory test	*Before exercise*	*Hours after exercise* 1	2	5	8	24	27
Urine							
Color	Yellow	—	red	red	red	red	yellow
Protein	0	—	+++++	—	—	—	0
Blood	0	—	+++++	+++++	+++++	+++	0
Cells	0	—	0	—	—	—	0
Casts	0	—	0	—	—	—	0
Serum creatine (mg. per cent)	0.6	1.5	2.6	1.9	1.1	0.4	0.5
Serum potassium (mEq.)	5.1	5.3	5.5	6.7	7.2	7.0	5.8
Electrocardiogram	N	N	N	LBBB	LBBB	LBBB	N

0 = Negative result — = Test not performed

nomenon could be observed and any associated laboratory abnormalities studied. In the morning, the patient was asked to squat as long as he could. This was repeated 5 times over a twenty-minute period. The patient was able to maintain this position for only one and one-half minutes each time because of pain. He complained of severe pain in the quadriceps muscles and developed marked sweating and muscular tremors but no spasm. The pain became quite severe, and the quadriceps muscles became hard to palpation bilaterally. Muscular pain and tenderness persisted for nearly nine hours. The patient voided 210 cc. of red urine two hours after onset of exercises and continued to void red urine for twenty-seven hours (Table 1). Urinalysis revealed 4+ albumin and 4+ benzidine test, although microscopy revealed no erythrocytes. The urine remained positive to the benzidine test for twenty-seven hours. An electrocardiogram taken six hours after exercise revealed the pattern of left bundle branch block, with peaked T waves suggestive of hyperkalemia. This pattern persisted for twenty-four hours. Blood chemistries, including carbon dioxide combining power, calcium, phosphorus, and creatinine, showed no significant change after exercise. However, blood creatine increased from 0.6 mg. to 2.6 mg. two hours after exercise and blood potassium, from 5.1 to 7.2 mEq. eight hours after exercise. These changes are summarized in Table 1.

Spectrophotometric examination of the urine revealed the alpha absorption band at 581 mμ., which is diagnostic of myoglobin. Characteristic absorption bands of porphyrins were not present. Porphyrins could not be detected in the urine by other routine tests. Microscopic examination of tissue obtained by muscle biopsy revealed segmental hyaline necrosis with coarse vacuolization of some fibers.

Subsequently, the patient was treated with 25 mg. of testosterone propionate and 100 mg. of thiamine parenterally, with some relief of muscle pain. He was then placed on a reducing diet and maintained on daily doses of thiamine and alpha-tocopherol.

Case 2. A 25-year-old white male was admitted to Parks Air Force Base Hospital because his muscles became tight, painful, and swollen after a relatively normal amount of exertion. These episodes were recurrent and started approximately five years before his admission; they were gradually becoming more frequent. Before his first attack, the patient participated in strenuous activity with no untoward effect. The patient was an electrician in the Air Force and noticed his first attack at the age of 20 while lying on his back, making repairs in a plane. He used his flexed right leg to maintain his position for several hours. After this, his thigh and leg became severely cramped, tense, and painful. Several hours later, painful swelling and weakness occurred in the right thigh and the patient passed dark red-brown urine. He was placed on bed rest with complete recovery. However, since that time numerous similar attacks involving almost all muscle groups had occurred. The quadriceps were most commonly affected, but the calves were also involved after moderately prolonged marches or walks; the back, buttocks, and neck, after swimming or lifting; and the arms, while carrying objects such as his tool kit for long periods. Occasionally, he had difficulty in releasing an object in his hand after the forearm became tense. Muscle groups above the neck were never involved. The urine turned dark brown on many of these occasions, usually after the more severe episodes of exertion. Associated symptoms at the onset of an attack would occur during more severe exertion. The patient would feel extreme generalized weakness and begin to hyperventilate. He felt as if he "couldn't get enough air" and experienced palpitations, sweating, light headedness, and spots before his eyes. Hours later, the tense, painful muscle would swell and the urine would darken.

Change of environment or extreme cold had no effect on his illness. The patient learned to mod-

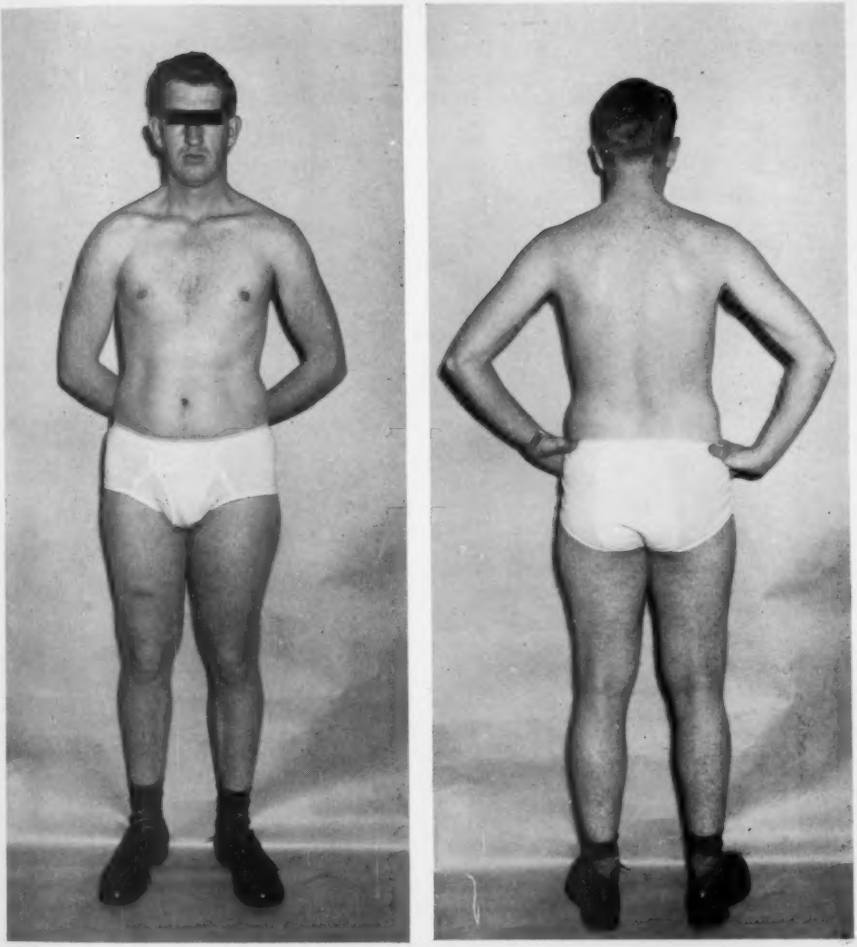

Fig. 1. Front and rear views of patient described in Case 2

erate his own activity so as not to precipitate attacks and curbed excessive exertion in all respects of his daily living, with resultant impairment of his social, marital, and military life. The family history was noncontributory. Both parents and all siblings were living and well. Previous illnesses included the usual infectious diseases of childhood and a report of "anemia" as a child. There were several episodes of tonsillitis in adult life, but none were associated with his present illness. He received only minor shocks while working as an electrician, and there was no report of excessive ingestion of fish or exposure to toxins. The remainder of the past history was essentially noncontributory.

On admission, general physical and neurologic examinations were normal. There were no signs of myotonia or other muscular abnormalities. The patient's physique was apparently normal with good development of both upper and lower extremities (Fig. 1).

Laboratory studies, including hemograms, hematocrit, sedimentation rate, bleeding time, and coagulation time, were normal. Serology, blood urea nitrogen, fasting blood sugar, total protein and albumin-globulin ratio, cholesterol, liver chemis-

TABLE 2
SIGNIFICANT LABORATORY FINDINGS—CASE 2

Laboratory test	*Before exercise*	*Hours after exercise*			
		6	*9*	*20*	*More than 48*
Urine					
Color	yellow	red brown	red brown	yellow	
pH	acid	acid	acid	acid	
Protein	0	++	+	0	
Blood	0	++	+++	0	
Cells	0	0	3 rbc	3 wbc, 2 rbc	
Casts	0	0	8	2	
WBC	8,850	—	9,800	—	
Serum transaminase	50	—	—	215, (135)	
Serum potassium (mEq.)	4.7	—	—	4.5	
Serum creatine (mg. per cent)	1.0	—	—	1.1	
BUN mg. per cent	17.2	—	—	14.4	
17-ketosteroids (24-hour urine)	—	—	—	—	30 mg.

0 = Negative result — = Test not performed

tries, and electrolytes (including potassium, calcium, chloride, phosphorus, and carbon dioxide) were likewise within normal limits. A five-hour glucose tolerance test was also completely normal. Admission urine was negative for protein, sugar, acetone, and microscopic examination. Tests for porphobilinogen were negative. Analysis for D-ribose was also negative. Other studies, including basal metabolic rate, radioactive iodine uptake, electrocardiogram, electroencephalogram, and roentgen films of the chest, skull, pelvis, and femurs were normal. Cerebrospinal fluid was under normal pressure and revealed no abnormalities of appearance, protein, cells, sugar, serology, or colloidal gold curve. Slit lamp examination was unremarkable.

After most of these initial studies were done, the patient was exercised late one morning. He walked approximately 400 ft. and then did 20 deep-knee bends. During and immediately after the exercises, the patient complained of cramps and a feeling of tightness of both quadriceps. He felt weak and was unable to flex his right knee. The only other objective change noted was some tenseness of the right thigh. However, approximately six hours later, the patient noted marked, tender swelling of the right anterior thigh and darkening of his urine. Examination at this time revealed a firm, tender, swollen right quadriceps that was fully 2 in. greater in circumference than the left. The knee and ankle jerks on the right were depressed, and there was weakness of the extremity in addition to the limitation of motion caused by pain. There were no sensory changes. The urine was dark red-brown, and laboratory examination was positive for protein and blood, although no cells were present. The findings are summarized in Table 2. Granular casts were present in later specimens, and the last positive specimen was obtained approximately nine hours after exercise. The next morning the urines were clear.

Other laboratory studies were performed on the morning after this episode, and there were no abnormalities of white blood count, differential, sedimentation rate, blood urea nitrogen, or electrolytes, including potassium. Blood creatinine was 1 mg. per cent on admission and 1.1 mg. per cent on the morning after exercise. However, it should be noted that specimens were not taken serially, as in Case 1, and there may well have been transient rise in these factors. Serum transaminase had a value of 135 units on the day following exercise (normal, up to 40 units). Subsequent examinations of the blood creatinine were within normal limits. Twenty-four-hour urine specimens tested for creatinine were 2 gm. and 2.1 gm., which are the upper limits of normal; urinary creatine was normal. Urinary 17-ketosteroid excretion was 30 mg. per twenty-four hours, which is slightly elevated.

Because the initial urine sample was not tested spectroscopically for myoglobin, the patient was observed for a period of two months and, on 5 separate occasions, was exercised in order to precipitate an attack and obtain spectroscopic verification of the disease. Each of these attempts failed. The amount of exertion used was up to 2 to 3 times that used to precipitate the attack on the initial occasion. They were all done very early in the morning before breakfast. The patient had been on bed rest most of the time. After the exercise, the patient occasionally noticed pain of the buttocks or thigh with minimal or no swelling and no darkening of the urine.

He was given leave for one month and, upon returning to the hospital, reported that he had had 2 episodes of more severe muscle cramps and that these occurred when several hours of mod-

erate activity preceded more strenuous activity. Therefore, upon returning to the ward, he was premedicated with sodium bicarbonate, 2 gm. every four hours, to alkalinize his urine and keep the myoglobin from precipitating in the renal tubules. The patient was then exercised again in the late morning, after he had had several hours of routine ward activity and walking. After only 10 deep-knee bends, the patient had an attack similar to his initial one. There was subsequent painful swelling of the thighs, associated with weakness and darkening of the urine about four hours later. Spectroscopic examination revealed the presence of myoglobin. Other laboratory tests showed essentially the same changes that occurred during the previous episode. The serum transaminase rose from 50 units during the state of moderate activity to 215 units one day after exercise. The serum did not change color as occurs in hemoglobinuria. The urinary findings were similar to that described in Table 2. Muscle biopsy of the right quadriceps was considered to be normal, and semiquantitative histochemical studies for glycogen were within normal limits.

The patient was not treated with drugs but advised to moderate his activity according to his own tolerance and to take sodium bicarbonate, if an attack occurred, to prevent renal complications secondary to precipitation of the myoglobin in the renal tubules.

DISCUSSION AND REVIEW OF THE LITERATURE

Clinical review. These 2 cases bear a striking clinical similarity to each other. The condition started at the ages of 18 and 20, respectively, and followed a relatively long, chronic course of repeated attacks of muscular involvement, which were quite definitely precipitated by exertion. Immediately after exertion, muscular symptoms appeared; within two to five hours, myoglobin was found in the urine. Thus, to the authors, the syndrome seemed to be well delineated. However, after an intensive review of the literature, it soon became apparent that the cases reported represented a heterogeneous group in which myoglobinuria was suspected or proved. In order to establish possible relationships among the cases, the clinical data available were tabulated (Table 3). The criteria for including cases in the series included spectroscopic verification of myoglobin in the urine (Table 3, verification, MY), pathologic examination of muscle tissue (P), and the clinical course of the patient (CL). In the first 4 cases, the method of spectroscopic identification of myoglobin was not yet known and the urinary pigment was reported as hemoglobin (HB). The last 2 cases (No. 44 and 45) were reported as cases of march hemoglobinuria, but, because of their clinical course and the lack of spectroscopic verification, the authors agree with Hipp and Shukers[29] that these cases can be accepted as paroxysmal paralytic myoglobinuria. Thus, a total of 45 cases were tabulated. (Since this tabulation, 6 other cases [No. 46-51] have been reported in the literature[63–66] but are not included in the present discussion). The clinical variables were chosen for the purpose of comparing and differentiating clinical groups. The major difficulty that arose was the incompleteness of the data available. For example, the cases of Millikan (No. 7) and of Schaar and associates (No 18) are presented and do not supply adequate information for complete tabulation. Most of the reports do give adequate information for such a study.

The age of onset of the disease as well as its duration was extremely significant and will be discussed below. A definite family history of a similar or related disease was noted in 12 cases. In 9 of these, there was a history of relatives having definite episodes of darkening of the urine; these included 3 brothers reported by Hed (No. 12, 13, and 14) and a brother and sister reported by Bowden and associates (No. 36 and 39, Table 3, Family History, MY). However, in the remaining 3 cases, the family history was not one of myoglobinuria but that of a muscular disorder usually diagnosed as a muscular dystrophy. These include the cases of Acheson and McAlpine (No. 22), Wissler (No. 16), and Louw and Nielsen (No. 9, Table 3, Family History, D). In the last mentioned case, the authors made a thorough investigative study of the patient's family history and clearly defined a sex-linked recessive trait that only occurred in males and was manifested clinically by what appeared to be muscular dystrophy. No history of darkening of the urine could be established in any of these relatives, and the patient himself had no atrophy.

The relationship of these attacks to exertion was striking and unequivocal in some cases and completely lacking in others. In fact, this was the most impressive differentiating factor noted in our cases, as well as some of those described in the literature. Thus, in the categorization of the cases a plus (+) signifies an unequivocal

TABLE 3
REPORTED CASES OF MYOGLOBINURIA

No.	Author	Age	Sex	Duration of symptoms (years)	Family history	Exertion	Group	Episodes	Associated illness	Fever or leuko.	Atrophy	Uremia	Fatality	Verification HB	Verification MY	Verification P	Verification CL
1.	Meyer-Betz ('10)[1]	13	M	4	0	0	II	Multiple	0	+	+	0	0	HB			CL
2.	Paul ('24)[6]	42	F	–	0	0	II	1	GI, PN, myositis	+	0	+	+	HB		P	
3.	Günther ('24)[7]	54	M	–	0	0	II	1	URI, myositis	+	0	+	+	HB		P	
4.	Hittmair ('25)[8]	43	F	2	+MY	+	I	Multiple	GI (once)	±	+	0	0	HB			CL
5.	Debré et al. ('34)[9]	6	F	3¼	0	0	II	Multiple	0	+	0	0	0				CL
6.	Huber et al. ('38)[10]	4	M	–	0	±	II	1	URI	+	0	+	0				CL
7.	Millikan ('39)[11]	Adult	?	?	?	+	I	Multiple	?	?	?	?	0		MY		CL
8.	Bywaters & Dible ('43)[12]	24	M	*10+	0	+	I	Multiple	URI (once)	+	0	+	+			P	CL
9.	Louw & Nielsen ('44)[13]	10	M	6	+D	±	II	Multiple	0	0	0	0	0		MY		CL
10.	Scherwin ('45)[14]	38	M	5	0	+	I	Multiple	0	0	+	0	0				CL
11.	DeLangen ('46)[15]	37	M	–	0	+	III	1	Trauma, pressure	+	+	+	0		MY		
12.	Hed ('47–'55)[16]	30	M	16	+MY	+	I	Multiple	0	+	0	0	0		MY		CL
13.	Hed$_2$ ('47–'55)[16]	29	M	13	+MY	+	I	Multiple	0	+	0	0	0		MY		CL
14.	Hed$_3$ ('47–'55)[16]	35	M	15	+MY	+	I	Multiple	0	+	0	0	0				CL
15.	Kreutzer et al. ('48)[17]	39	M	20+	0	+	I	Multiple	0	0	+	0	0		MY		CL
16.	Wissler ('48)[18]	6½	M	–	+D	±	II	1	URI	+	0	0	0		MY		
17.	Iversen ('48)[19]	55	M	–	0	+	I	1	Seizures	?	0	+	+		MY		
18.	Schaar et al. ('49)[20]	23	M	?	+MY	?	?	?	?	?	?	+	+		MY	P	
19.	Buchanan & Steiner ('51)[21]	4	M	2	0	±	II	2	URI, encephalitis	+	0	0	+		MY	P	
20.	Jasinski & Brütsch ('52)[22]	43	M	–	0	?	III	1	Pressure	?	?	+	0		MY	P	
21.	Touze & Thierry ('52)[23]	20	F	–	0	0	III	1	Pressure	+	0	+	0				CL
22.	Acheson & McAlpine ('53)[24]	30	M	*22	+D	+	I	Multiple	0	0	+	0	0		MY		CL
23.	Stokes ('53)[25]	15½	F	–	0	0	II	1	URI	?	0	?	+		MY		
24.	Elek & Anderson ('53)[26]	41	F	–	0	0	III	1	Trauma, surgery	0	0	0	0		MY		
25.	Spaet et al. ('54)[27]	23	M	*10+	0	+	I	Multiple	0	+	0	+	0		MY		CL
26.	Horman ('54)[28]	64	M	–	0	0	II	1	?, hepatic disease	0	0	+	+		MY		
27.	Hed[4] ('55)[16]	40	M	9	0	0	II	Multiple	?, Xmas	+	0	+	0		MY		
28.	Hed$_5$ ('55)[16]	53	M	3	0	0	II	Multiple	0	+	0	+	+		MY	P	
29.	Hed$_6$ ('55)[16]	13	M	*10	0	+	I	1	0	0	+	0	0		MY	P	
30.	Hipp & Shukers ('55)[29]	31	M	10	0	+	I	Multiple	EST (once)	0	?MYO	0	0		MY		CL
31.	Schaar$_2$ ('55)[30]	9	M	–	0	±	II	1	URI, PN.	+	0	0	0		MY		
32.	Berenbaum et al. ('55)[31]	10	F	6	0	0	II	2	Surgery (once)	+	0	0	0		MY		
33.	Reiner$_2$ et al. ('56)[24]	42	M	23	0	+	I	Multiple	Multiple	+	0	0	+	HB		P	CL
36.	Bowden et al. ('56)[25]	4	M	3	+MY	II	0	GI	GI, URI, surgery	+	+	+	0		MY		CL
37.	Bowden$_2$ et al. ('56)[25]	8½	F	4½	0	0	II	Multiple	URI	?	0	0	0		MY		

31. Schaar, ('55)[30]	9	M	–	0	+	I	Multiple	EST (once)	0	?MYO	0	0		MY		CL
32. Rotenberg et al. ('55)[31]	10	F	?	0	±	II	1	URI, PN	+	0	0	0		MY		
33. Reiner, et al. ('56)[32]	42	M	25	0	0	II	3	Strenuous exercise	+	+	0	0		MY		
34. Bowden, et al. ('56)[33]	4	M	3	+MY	II	0	GI	Multiple	+	0	0	+	HB		P	CL
35. Bowden, et al. ('56)[33]	8¼	F	4½	0	0	II	Multiple	GI, URI, surgery	+	+	+	0		MY		CL
36. Bowden, et al. ('56)[33]	6½	M	–	0	0	II	1	URI	?	0	0	0		MY		
37. Bowden, et al. ('56)[33]	4	F	1	+MY	0	II	2	0	?	0	0	+		MY	P	
38. Pearson et al. ('57)[34]	57	M	•37	0	+	I	Multiple	0	0	+	0	+	0		MY		CL
39. Watson & Ainbender ('57)[35]	6	M	1	0	0	II	2	0	+	0	+	+	0		MY	P	
40. Present Case 1 ('58)	52	M	•34	0	+	I	Multiple	0	0	0	0	0	0		MY		CL
41. Present Case 2 ('58)	25	M	5	0	+	I	Multiple	0	0	0	0	0	0		MY		CL
42. Fleming & Kinsman ('45)[36]	23	M	7	0	+	I	Multiple	URI, PN (once)	0	0	0	0	0				CL
43. Chalken et al. ('53)[37]	22	M	2 mo.	+MY	+	I	Multiple	0	0	0	0	0	0				CL
44. Berg & Frenkel ('58)[38]†	22	M	2	0	0	II	Multiple	URI, fever, surgery	+	0	0	0	0		MY		CL
45. Fitz$_1$ ('57)[39]†	34	M	–	+MY	0	II	1(?)	URI	+	0	0	0	0				CL
46. Fitz$_2$ ('57)[39]†	31	M	?	+MY	0	II	Multiple	—	0	0	+	+	0				CL
47. Fitz$_3$ ('57)[39]†	24	F	–	+MY	0	II	1	URI	+	0	+	+	0				CL
48. Segar ('59)[40]†	15	M	–	0	0	II	1	Infection	+	+	+	0		MY			CL
49. Kaufman and Barry ('59)[40]†	42	F	3 mo.	0	0	II	1	0	+	0	0	+		MY	P	

Legend and discussion in text
•Muscular symptoms preceded those of myoglobinuria in these cases by several years.
†Reviewed after completion of tabulation

causal relationship of exertion, and mainly exertion, to the attacks of myoglobinuria, while plus-minus (±) signifies occasional or minimal relationship of exertion as a causal factor. A zero (0) represents no relationships to exertion (Table 3, Exertion). The exertion involved was not always extremely severe but usually was strenuous. The severity of the attack usually correlated with the degree of exertion in those cases in which exertion was the precipitating factor. In a case described by Reiner and associates (No. 35), the patient had repeated grand mal seizures, after which he would have myoglobinuria and the associated muscular symptoms. The exertion in this case was caused by the seizures. Another patient, reported by Hipp and Shukers (No. 30), had an episode of myoglobinuria after receiving electroshock therapy for his depression. After this, the episodes could be precipitated by crouching and other exercises. Iversen's case (No. 17) had his fatal first episode during an attack of status epilepticus. These last 3 cases are specifically mentioned because of the nature of the exertion involved. The other cases precipitated by exertion seemed to be clinically very similar to the 2 described in the present report. Therefore, exertion was the factor that was used primarily to separate the cases into groups. Group I consisted of 21 patients in whom the myoglobinuria was unequivocally related to exertion. Group II consisted of 19 patients in whom exertion was not the primary factor and no definite traumatic cause for the myoglobinuria could be established. (The 6 recently reported cases would all be classified in Group II.) Group III included 4 cases in which trauma or pressure seemed to be primarily responsible for the myoglobinuria. These last 4 cases would not fall into the category of myoglobinuria of unknown etiology, although occasionally reported as such, for example, Elek and Anderson (No. 24). Unfortunately, data available on the case reported by Schaar and associates (No. 18) were inadequate for the present grouping. In the remainder of the discussion, all the clinical variables will be compared in terms of group I and group II (Table 3 and Fig. 2).

All but one patient (95%) in the exertional group were males, while there were 68% males

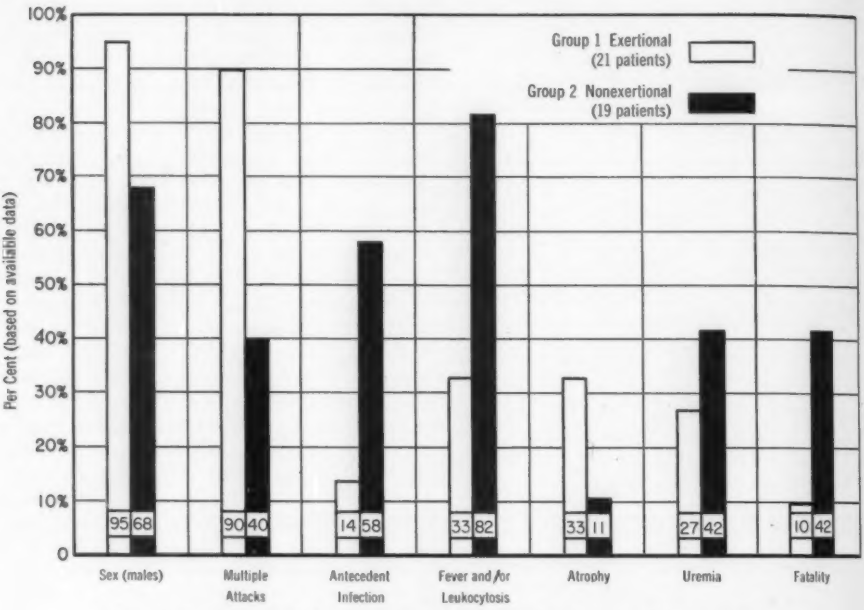

Fig. 2. Comparison of clinical features of exertional and nonexertional patients

in the nonexertional group (Fig. 2). The number of episodes or attacks of myoglobinuria that the various patients had seemed significant, but, because of the lack of exact data, they were categorized only as having 1, 2, and multiple attacks. It will be noted that, in group I, 90% of the cases (19 patients) are reported as having multiple attacks (Fig. 2). Usually, they all had many more than 3 episodes and were similar to the multiplicity of attacks described in the 2 cases presented. The 2 exceptions include the patient previously described, who died after being in status epilepticus (No. 17), and a 13-year-old boy described by Hed (No. 29). This last patient was followed for about a year but was advised to carefully avoid exertion for fear of precipitating another attack. In group II, the nonexertional group, multiple attacks occurred in approximately 40% (7 patients); 8 patients had single episodes. Of these, 4 ended fatally and, of those that survived, several were followed for about a year without repeated attacks. There were 4 patients in group II who had only 2 attacks each, and it was felt that these were not sufficient to warrant the term multiple, since they appeared clinically comparable to the single episodes. In fact, 2 of the 7 cases in group II reported as having multiple episodes had only 3 attacks each, usually related to an acute infectious process. This was reported in the case of Bowden and associates (No. 37), and, in the case of Debré and associates (No. 5), the patient was reported to have been followed many years without a subsequent attack.[9]

In many cases of group II, an acute infectious process seemed to be associated with the onset of the attack of myoglobinuria (Table 3, Associated Illness). The most common of these were upper respiratory infections (URI), occasionally associated with pneumonia (PN). Infections of this type occurred in 11 cases. In 4 cases, a gastrointestinal infection (GI) occurred at the onset of myoglobinuria, and, in 2, the cause was proved to be bacillary dysentery. As noted in Figure 2, a history of an infectious process at the onset of the attack was present in almost 60% of the nonexertional cases (group II). In some of these in which

multiple attacks occurred, such as the case of Bowden and associates (No. 37), each attack was associated with an infectious process. In the exertional cases (group I), related infections occurred in a smaller proportion of cases (14%), and in these 3 cases the infection was severe only in the case of Bywaters and Dible (No. 8). In this case, previous attacks were always related to exercise alone and the last attack, which was related to infection, also proved to be fatal. Some of the patients had associated chronic diseases, including hypertension, diabetes, thyroid disease, hepatic diseases, encephalitis, and cerebrovascular disease. Although some authors considered these significant, no consistent or definite relationship to the myoglobinuria was ascertained. It is noteworthy that in 2 of the nonexertional cases, that of Paul (No. 2) and Günther (No. 3), a diagnosis of myositis was made. (After completion of this tabulation, the authors have been notified of 2 additional cases of verified myositis with proved myoglobinuria.) These data suggest that antecedent systemic infections as well as primary myositis may be considered as causal factors, especially in the nonexertional group.

Fever or leukocytosis was definitely present in 22 cases (+); in 2, there were minimal findings of this nature, which were of questionable significance (±), and, in 8, data were not given (Table 3). It can be seen from Figure 2 that, in the nonexertional group, 82% of the cases, where data were available, had fever or leukocytosis, while this occurred in only 33% of exertional group. The relationship of the fever or leukocytosis to infectious processes, when present, must be considered, but it also occurred at the onset of attacks in which no obvious infection was present.

Some degree of clinically observable atrophy was noted in 10 cases. Of these, 7 were noted in group I (33%) and 2 in group II (11%) (Fig. 2). The relationship of the atrophy to the attacks of myoglobinuria was definite in several patients. The onset of the atrophy followed severe attacks of myoglobinuria in the cases of Scherwin (No. 10) and Pearson and associates (No. 40). However, there were cases in which the onset of muscular symptoms and atrophy preceded by several years the onset of clinically observed myoglobinuria. This was recognized in the cases of Hed (No. 29) and Acheson and McAlpine (No. 22). Again, as in those cases with a family history of muscular disorders, the problem of the relationship of muscular dystrophy and myoglobinuria arose. A possible explanation that might satisfy the available facts is that subclinical myoglobinuria may occur, causing atrophy without frank attacks of myoglobinuria. This is supported by the fact that many attacks occurred before and in between episodes of frank myoglobinuria, in which muscular symptoms were present alone; also, the presence of atrophy was greater in exertional groups which, as will be noted, have a more chronic course. Against this thesis, however, is the fact that many group I patients had many severe episodes of muscle symptoms and myoglobinuria for many years and did not develop atrophy. The report of myotonia in the case of Hipp and Schukers (No. 30) may be related to muscular spasm, as described in our second patient. He also had difficulty in releasing objects, which was related to sustained muscular contraction after his hands were in use. This does not appear to be a true myotonia.

The most serious complication reported in these cases with myoglobinuria was uremia and renal failure. Whether the renal complication occurs because of occlusion of the renal tubules by the precipitated pigment or because of a reflexly decreased renal blood flow is still open to question; probably both factors are involved. Of the 45 cases listed, 18 had uremic episodes and, of these, 7 were fatal. Uremia occurred more commonly in the nonexertional group (42%) than in the exertional group (27%) (Fig. 2) and was commonly associated with infection and pressure injuries (group III, Table 3). This seems to be partially related to the difference in the mortality rates of the 2 groups. The number of deaths was significantly higher in group II (42%) as compared to group I (10%).

The incidence of the age of onset in the 2 groups is also highly significant (Fig. 3). This figure was available in 19 patients in each group. If we compare group I (open circles) and group II (solid circles) as to duration of symptoms and age of onset of the myoglobinuria, the differences between the 2 groups will become more apparent. In 16 (84%) of the

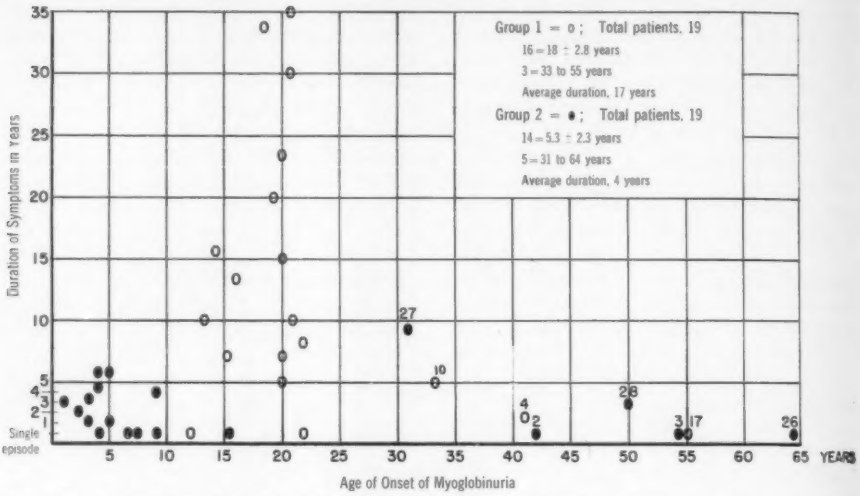
Group 1 = o ; Total patients, 19
16 = 18 ± 2.8 years
3 = 33 to 55 years
Average duration, 17 years
Group 2 = • ; Total patients, 19
14 = 5.3 ± 2.3 years
5 = 31 to 64 years
Average duration, 4 years
Duration of Symptoms in Years
Single episode
Age of Onset of Myoglobinuria
YEARS

Fig. 3. Comparison of age of onset of myoglobinuria and duration of symptoms in exertional (group I—O) and nonexertional (group II—•) patients

cases in group I, the exertional category, the onset began at an average age of 18 years with a mean deviation of ± 2.8 years. As can be seen by the narrow distribution of the large majority of open circles in Figure 3, the most common age of onset in this group obviously centers about late adolescence and early adulthood. The average duration of the period during which the patient had his multiple attacks is seventeen years. This is represented by the upward trend of the open circles in Figure 3. On the other hand, in group II, the nonexertional cases, 14 (74%) of the patients have their onset at the average age of 5.3 years with a mean deviation of ± 2.3 years. This is represented by the fairly tight grouping of most of the solid circles in Figure 3. The average duration of the period of multiple attacks was about four years. This is reflected by the relatively low position of the solid circles in the graph. In the exertional group (I), it will be noted that 3 cases are separated from the main trend. Scherwin's case (No. 10) has no other significant differential features when compared with the other cases of group I, except for the age of onset. It should be noted that, of the 3 exceptions, this patient is closest to the main body of group I. Hittmair's case (No. 4) is the only woman in this group and differentiates herself clearly. The third exception is the case of Iversen (No. 17), which, although included in the exertional group, differs markedly from the others. The patient, a 55-year-old man, was in status epilepticus for two days when he developed myoglobinuria; uremia followed, and the patient died. This was his only episode of myoglobinuria, and the history does not state whether the patient suffered any trauma during his status. This patient may very well belong to group III, although exertion was definitely an etiologic factor.

In group II, there were 5 exceptions to the majority, which had an age of onset during childhood. Paul's case (No. 2), a 42-year-old woman, and Günther's case (No. 3), a 54-year-old man, both had severe infections and were diagnosed as having myositis. Both of these patients had uremia and died. The case of Horman (No. 26) was a 64-year-old man who had signs of acute liver disease. He died after having uremia and a cerebrovascular thrombosis. The details of the onset of his disease were not available. From reviewing these 3 cases, it would seem that these single, fatal episodes of myoglobinuria were associated with acute infectious processes. In 1 case of Hed

(No. 27), the history is somewhat bizarre. The patient was a 40-year-old man who noticed the onset of attacks of myoglobinuria and lower extremity muscle pain just before the beginning of Christmas for six successive years. Precipitation by exertion was denied. One cannot help questioning the history. Clinically, except for the fact of exertion, the patient would belong in group I. The last case (No. 28) mentions no definite history of exertion or infection related to his 3 attacks. These exceptions do not seem to invalidate the main trend revealed by the majority of the cases. Therefore, the evidence apparently justifies the division of these reported cases of myoglobinuria into 2 distinct groups. Group I included cases that were definitely precipitated by exertion, in which 95% of the cases were males and 90% of the attacks were multiple; in 84% of these cases the age of onset was approximately 18 years, and it was a longstanding chronic disease lasting up to thirty-seven years. Occasionally, fever or leukocytosis occurred at the onset of an attack. Atrophy and uremia were common complicating factors, but the over-all mortality was relatively low (10%). Group II included cases that were not definitely precipitated by exertion, although occasionally exertion was a related factor; the most prominent causal factor seemed to be a related infection in 58% of the cases. In this group, 68% were males and, in 73% of the patients, the attacks were single or recurred just once. In the majority of cases, the age of onset was during childhood. If the individual suffered multiple attacks, it was for an average duration of four years. The disease was often acute and severe. The onset was more commonly associated with fever or leukocytosis than in group I, and the complications also included atrophy and uremia. However, the atrophy was less common and the uremia more common in this group as compared to group I. The mortality (42%) was significantly higher in this, the nonexertional group (summarized in Fig. 2). Hereditary factors have been implicated in several cases of both groups.

Previous attempts at classification of this disease have had serious deficiencies,[16,22,40] probably due to the fact that the number of cases reported have been too few to permit significant analysis. More recently, as the number of reported cases has been increasing, the differential features of the groups as defined in this report have become more obvious. In 1956, Bowden and associates[35] reported 3 cases in children and mentioned a fourth, all of the nonexertional variety. The present study substantiates the thesis of these authors that there are at least 2 clearly defined disease entities. It is suggested that the term *paroxysmal paralytic myoglobinuria* be reserved for those cases precipitated by exertion (group I) and that the term *idiopathic* or perhaps *toxic myoglobinuria* be reserved for the nonexertional cases (group II). Further reasons for this terminology will be mentioned below.

Laboratory studies. A survey of the significant laboratory studies in these cases of myoglobinuria at times discloses conflicting reports similar to those observed in reviewing the clinical data. However, if we adhere to the previously described grouping, some aspects of the laboratory data, especially the pathologic studies, become more significant.

The reports of muscle histopathology were reviewed in 25 of the cases. Several factors must be considered before these findings are presented. The picture of the disease process as represented by histologic studies will vary radically depending on the acuteness and severity of the disease as well as the time at which the biopsy is taken. Another limitation in such a review is the variety of terms used to describe a given specimen, making it difficult to adequately compare the pathologic material reported. The results of histologic examinations are quantitatively approximated in Figure 4 as normal, moderate, and severe degenerative changes. The moderate degenerative changes described were usually focal or scattered in nature and included poor staining, occasional loss of striations, and sarcolemmic proliferation. In addition to these, chronic changes similar to those found in muscular dystrophy were included in the moderate group. Changes that were most often acute and involved relatively large masses of muscle with loss of striation, fragmentation, vacuolization, hyalinization, cloudy swelling, and pale, waxy degeneration described as a "fish flesh" appearance were considered as severe degenerative changes.[41] As will be noted in Figure 4, 5 of the cases in group I had normal muscle

histology at the time of biopsy and 5 showed moderate degenerative changes; 2 of the latter were described as compatible with muscular dystrophy. The only patient in group I with severe degenerative changes was reported by Bywaters and Dible,[12] and he had an acute upper respiratory infection associated with his final attack of myoglobinuria. In group II, 7 out of 11 patients tabulated had severe degenerative involvement of muscle and 3 had moderate degenerative changes. Only 1 was normal, and no case exhibited changes compatible with muscular dystrophy. The 3 cases not tabulated were either unclassified or in group III. These findings tend to support the impression that the patients with paroxysmal paralytic myoglobinuria, in whom the attacks were precipitated by exertion, had less severe muscle involvement in comparison with the cases with toxic myoglobinuria, in which an associated infection was usually related to the onset. As noted, the exertional case with the most severe degenerative findings had an associated infection.

In the remainder of the laboratory studies, data are thus far inadequate to evaluate statistically in the present grouping. In those cases in which quantitative studies were done on the myoglobin content of the muscle, it was usually found to be decreased,[16,31] whether degenerative changes were present or not.

Histochemical studies of Berenbaum and associates[31] on their case revealed a complete loss of glycogen from diseased muscle fibers and an almost complete loss from normal fibers. This supports the findings of Bowden and associates[35] of an increase in blood glycogen after an acute episode. Other laboratory tests revealed that many other components of the disrupted muscle fiber were released into

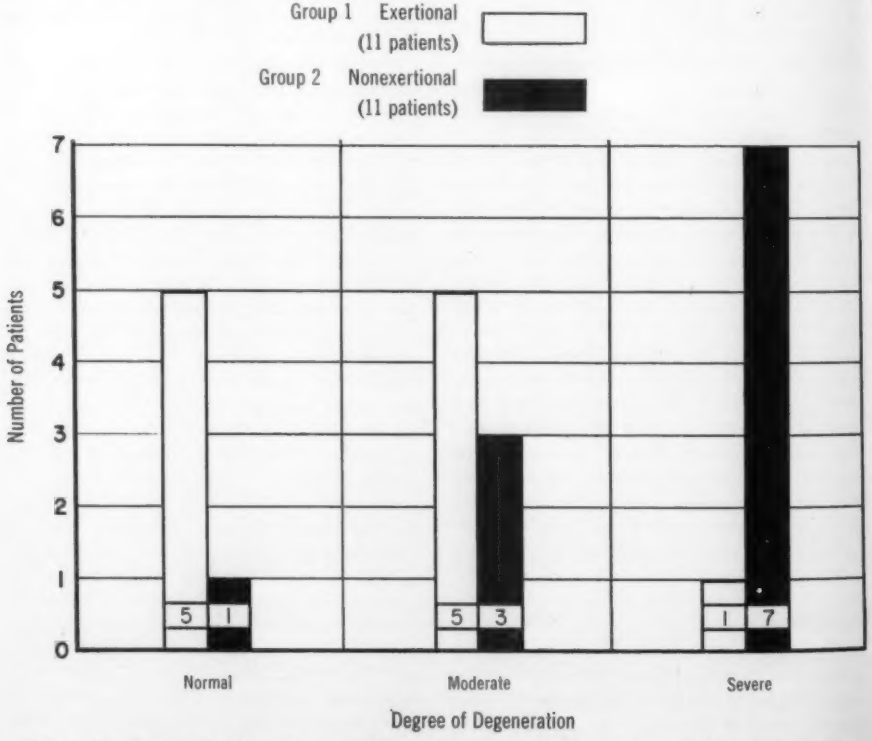

Fig. 4. Comparison of pathologic muscle findings of exertional (I) and nonexertional (II) patients

the circulation. The amino acid excretion in the urine was noted to be markedly elevated in 1 case.[35] Studies of lactic acid changes in the blood, however, did not show a definite or significant increase.[17,36]

Numerous enzymes are also released from the involved muscles. In our second case, the serum transaminase was abnormally high in the state of normal activity and was markedly elevated twenty-four hours after exercise (Table 2). In the study of Pearson and associates,[36] there were concomitant rises in serum transaminase, aldolase, and phosphohexoisomerase within two to five hours after exertion. These were normal within four days after exercise. These findings probably represent the results of acute muscle disruption. Blood transaminase studies may be one of the simpler diagnostic tests that can be used as an adjunct in diagnosing and following the course of the disease.

There were no significant changes of electrolytes reported with the exception of serum potassium level. In our first case, there was a significant transient elevation of serum potassium. However, in the second case, although serial determinations were not done, postexercise serum potassium levels were normal. Elevation of serum potassium similar to that in the first case has been reported.[11] However, serial studies of others[15,27,40] failed to reveal any change in serum potassium level after exertion. In fact, Acheson and McAlpine[24] found serum potassium levels in their case that were lower than normal after exertion. It has been postulated that the potassium elevation represents an associated renal dysfunction rather than the muscular disturbance itself. In most cases in which the potassium was elevated, uremia had occurred. The relation of the changes of the serum potassium to muscular disruption deserves further study.

Louw and Nielsen[13] were the first to describe the changes of creatine and creatinine metabolism in this disease. Most, but not all, investigators reported an increase of urinary creatine excretion and the concommitant decrease of urinary creatinine. The serum levels of creatine usually were increased after an attack. This is clearly shown in the serial studies done in our first case. Since the findings of increased urinary creatine excretion along with a decreased creatinine excretion occur in many muscular diseases, these findings have been compared with those seen in the cases of muscular dystrophy. According to Milhorat,[42] the amount of creatinine excreted as an end product of muscle metabolism is approximately proportional to the degree of functioning muscle mass, while the creatine that is utilized by muscle is excreted in greater quantities as muscle function decreases. Thus, creatine excretion may not be a product of muscle breakdown per se but a decreased utilization due to muscle malfunction, related to constant creatine production elsewhere. It is probable that the creatinuria is related to both mechanisms and does not necessarily prove a definite relationship between the myoglobinurias and muscle dystrophy, although it is suggestive.

Several authors have mentioned abnormal glucose tolerance curves in their cases.[16,36] This was also true in our first case. It has been postulated that abnormal glucose metabolism may be a primary factor in this disease. However, in the majority of the cases tested, including our second case, normal glucose tolerance tests have been the rule. This would suggest that this is probably an incidental finding, although the finding of Hed that low carbohydrate diet could act as a precipitating factor and caused myoglobinuric attacks in his 3 cases demands further study in this direction.

The 17-ketosteroid excretion has been reported to be elevated in several cases.[14,24,31,35] This was usually higher after the acute episode, although occasionally the elevation persisted. In our second case, the 17-ketosteroids also were moderately increased. It seems likely that these changes were an effect rather than a cause of the disease.

MYOGLOBINURIA IN OTHER CONDITIONS

Historically, paralytic myoglobinemia of horses has been known for over one hundred years.[43] It is particularly significant in the present study because Meyer-Betz's knowledge of this entity led to his first recognizing and reporting the condition of paroxysmal paralytic myglobinuria in man.[1] In horses, the disease is associated with paralytic manifestations, especially of the lumbar and hind limb muscles, followed by myoglobinuria. A hereditary factor may exist, since it occurs mostly in heavier work breeds

and less in thoroughbreds. Horses between the ages of 5 to 8 years are most susceptible, and both sexes are equally effected. The symptoms usually appear following a short period of inactivity (about five days), during which the animal ingests a rich carbohydrate diet and then performs vigorous and heavy sustained work. Stiffness and weakness of the hind limbs with tremor of the involved parts and generalized sweating are noted soon after activity begins. The horse collapses and is unable to rise. The paralyzed muscles at first are rigid and the following day are soft. There is a low grade fever, and, soon after the onset of symptoms, there is acute urinary retention and the catheterized urine is red or brown in color. The urine contains protein, casts, and a few red and white cells. Spectroscopic examination of the urine reveals the pigment to be myoglobin. The paralytic manifestations usually persist for two of three days and are followed by recovery. Relapses tend to occur in animals returned to work too soon after apparent recovery. Some degree of renal insufficiency usually occurs, but myoglobinuria is generally absent after the third day.

The etiology and pathogenesis remain obscure. It is generally assumed that the basic cause is a myogenous autotoxin resulting from an excess of some product of muscular activity.[43–45] This may be related to changes of blood flow in muscle during vigorous exercise, relative increase of muscle oxygen requirements, and the excess of glycogen, as well as the accumulation of lactic acid or other end products of active muscle metabolism.

The involved muscles have the appearance of "fish flesh." Microscopic examination reveals absent striations within four hours after the onset of symptoms. Hyaline, waxy, and fatty degeneration may also be seen. In more advanced stages, disintegration and cleavage of the protoplasm, disruption of the sarcolemmic sheaths, and round cell infiltration of the surrounding connective tissue are noted. These pathologic changes are strikingly similar to those noted in man.

In contrast to the myoglobinemia of horses, in which the significance of exertion in producing the clinical picture is unequivocal, in man, Haff disease is a form of myoglobinuria in which exertion is not a primary factor. Haff disease was first reported in 1924[2] and is unique because it occurs only in epidemic form in certain localities (Germany, East Prussia, Sweden, and Russia). The symptoms almost always develop after eating fish, especially eel and burbot, although it does not occur in all adult individuals on this diet. Both sexes are equally affected, and it is infrequently seen in children. During epidemics, the morbidity and mortality of fish, birds, foxes, and cats are unusually high.

The symptoms usually appear during ordinary muscular activity, about eighteen hours after eating fish. At first, the individual develops painful muscles, usually of the arms and calves, soon followed by generalized severe muscular pains. The patient complains of being stiff, and the muscles are exquisitely tender but have the consistency of normal resting muscle. Two to four hours after the onset of symptoms, the patient voids brownish-black urine that contains protein, casts, occasional red and white cells, and myoglobin. The patient usually remains afebrile and shows a moderate leukocytosis. Recovery usually occurs in two to three days. However, some degree of muscular tenderness and generalized tiredness persist for several days. The disease may occur with varying degrees of severity, and, in fatal cases (mortality rate, 1%), death results from renal failure and uremia. Atrophy does not seem to be associated with the disease. Histologic findings in the muscle and kidneys are similar to those reported in other types of myoglobinurias. Fatal cases show severe degenerative changes of muscle as well as renal tubular necrosis ("myoglobinuric nephrosis").

The clinical data in Haff disease suggest an exogenous toxic factor, although a constitutional predisposition may exist. Extensive research has not disclosed the exact nature of this toxic factor, but the evidence tends to strongly support its presence. Therefore, based on the authors' classification in terms of clinical groups, it would appear that the pathogenesis of the disease in horses is more closely related to those cases in the exertional category (group I) whereas Haff disease, while not identical, seems more closely related to the nonexertional (or possibly "toxic") category (group II).

The myoglobinuria associated with crush in-

juries is basically due to ischemic muscle necrosis from compression over a prolonged period of time. Similarly, prolonged occlusion of a main artery of an extremity may produce ischemia of muscle that will result in a comparable clinical syndrome.[3,4]

In the crush syndrome, the patient initially has severe pain for a short time followed by numbness of the involved part. The skin over the site of trauma is erythematous and sharply demarcated. The affected extremity is swollen, hard, paralyzed, and insensitive to pain. Later, the hardness subsides and the tissue has a "doughy" consistency. The patient usually voids within a few hours after the injury. The urine is highly acid and smoky, containing myoglobin, abnormally high amounts of potassium, creatine, and some casts but no erythrocytes. The urine is usually free of pigment within one or two days. Thereafter, the patient shows some signs of renal insufficiency. According to Bywaters,[3] this may be due to both mechanical blocking by the pigment and tubular dysfunction. Approximately two-thirds of the patients with crush injuries usually die within the first week. In patients who recover, the extent of the muscle necrosis is much less than in fatal cases. In these patients, the damaged muscle never fully recovers if complete ischemic necrosis has occurred. Regeneration of muscle fibers occurs in patients with less severe muscle damage. In autopsied or operated cases, the compressed muscle grossly appears pale and swollen, at times mottled with hemorrhages. The muscle fibers are opaque and friable, and there is necrotic tissue that is sharply demarcated from adjacent normal tissue. Microscopic examination reveals loss of muscle fiber nuclei and vacuolization but usually without loss of cross striations.

Since the incidence of myoglobinuria is much higher in crush injuries than in occlusion of the main vessel of an extremity, it seems reasonable to assume that the degree of ischemia is the most important single factor in the production of myoglobinuria. In the crush syndrome, compression is more apt to result in complete ischemia, and, in arterial occlusion, a collateral circulation may prevent complete ischemia from occurring. Further, the factor of reestablishing return circulation from the involved region is also of great importance, because this is the only way the released myoglobin may reach the general circulation.

The time factor is extremely important, since the crush must exist for a period of hours to cause sufficient ischemia for the syndrome to develop. It should be emphasized that the main causal factor related to the myoglobinuria appears to be a relative decrease of oxygen to the involved muscles. This is certainly comparable to the relative oxygen deficit observed in equine myoglobinemia during exertion and may be the significant factor in all myoglobinurias, as will be discussed later.

Fischer and Rossier,[5] described 4 cases of high voltage electric shock in which the victims survived and later developed myoglobinuria. The shocks were of the order of more than 40,000 volts, and the patients seemed to have escaped with burns of moderate to severe degree. About one to two days later, 2 of the patients had darkening of the urine and then went into uremia and died. Myoglobin was found in the urine, and the pathologic changes in the muscle and kidney were similar to those observed in the crush syndrome. In the 2 patients who survived, there was marked weakness of the extremities associated with degenerative muscular changes and myoglobinuria. In these cases, the pathologic picture may be explained by postulating extreme muscular activity induced by the electric shock with a relative oxygen deficit.

PATHOPHYSIOLOGY OF THE MYOGLOBINURIAS

Previous reports on paroxysmal paralytic myoglobinuria state very little as to the possible pathologic mechanisms that may be involved in this disease. Several authors[35,36] assumed that the myoglobin in itself is not a major or direct factor in the disease but only a byproduct of generalized acute cell disruption. Others have considered the possibility that the main defect is in the myoglobin.[31] The present review of the clinical, biochemical, and physiologic data available on myoglobin and the myoglobinurias strongly suggests a defect in oxygen utilization in striated muscle as being the underlying common denominator in this syndrome. The defect in oxygen utilization could be related to decreased myoglobin content or abnormally decreased ability in oxygen transfer from the hemoglobin to the

myoglobin or from the myoglobin to the oxidative systems in the cell. The distribution, properties, and function of myoglobin strongly tend to support this thesis. Its molecular weight is about 17,000, and it has a single hemin group related to the globin portion. While the hemin portion is identical to that found in hemoglobin, the globin fraction is different in amino acid composition and structure.[40,46] Myoglobin combines with the oxygen from hemoglobin at even relatively low oxygen tensions and thus serves its function as an oxygen reservoir for the muscle cell.[11] The striated muscles that function in long, sustained, forceful contractions are those with the greatest concentration of myoglobin (red muscle). The quadriceps, gastrocnemius, and back muscles are examples. These muscles are mainly affected in the myoglobinurias. Striated muscles that undergo more rapid contractions or strong contractions with longer intervals in between depend less on myoglobin and more on the cytochrome systems directly.

The biochemical events in the muscle cell can now be considered in terms of carbohydrate utilization and its relationship to oxygen supply. Available carbohydrate (see addendum) enters into these reactions to produce energy for the maintenance of cell structure and function, which is primarily in the form of adenosine triphosphate (ATP).[47–49] The ATP is produced by means of the anaerobic and aerobic cycles within the cell; the aerobic cycle produces ATP in a far more efficient manner than the anaerobic cycle. Thus, the main production of ATP is dependent on the available oxygen to the aerobic cycle, which in turn is dependent on the adequate function of available myoglobin. During the resting stage, the rate of ATP production by the aerobic cycle is not high and, in fact, much of the cell's requirements may even be met by the anaerobic cycle. However, during activity, the ATP requirements rapidly rise and the activity of the aerobic cycle with its oxygen requirements also rises. The rate of oxygen expenditure of the myoglobin is 1% per second in the resting state and 10 to 40% per second during tetanic contraction, with the maximum expenditure occurring within one second and restitution to resting value within ten seconds after the contraction ends (Millikan in Biork[40]). Thus, in maximally prolonged contractions of striated muscle, the need for normally functioning myoglobin in adequate amounts is evident. Another result of malfunction of the aerobic cycle of possible significance would be an increase in the amount of end products of the anaerobic cycle which could not be removed.[50]

A defect of oxygen utilization related to abnormal or deficient myoglobin could account for many of the clinical and pathologic features of exertional myoglobinuria (group I). This defect would cause a relative decrease of ATP production during exertional states and would lead to malfunction of the myofibril, manifested by paresis. If severe ATP deficit occurred, secondary disruptions of cellular structure and membrane could occur, with subsequent discharge of the contents of the cell, including myoglobin, into the circulation, thus resulting in myoglobinuria. Perhaps the increased resistance to attacks after rest in our second patient is related to the replenishment of abnormal myoglobin with oxygen. As stated, the oxygen deficit is relative to the adequacy of the myoglobin and the degree of oxygen requirements of the active muscle cell, and, in normal individuals, myoglobinuria may occur under conditions of intense muscular activity. Long distance runners may excrete myoglobin in the urine after extreme exertion.[51] In those cases of myoglobinuria secondary to electric shock, the extreme muscular activity related to the shock may deplete the oxygen from the myoglobin and create a relative local oxygen deficit leading to the syndrome. In crush injuries and arterial occlusion of muscle, the local anoxia is not related to exertion or myoglobin but is due to circulatory factors. In Haff disease or the toxic myoglobinurias, minimal activity would be sufficient to produce the syndrome because, in these conditions, a toxic factor affecting the myoglobin and thus oxygen utilization is implicated, although a hereditary predisposition may also exist. Fever alone would increase the oxygen requirements of the cell. Experimental evidence in animals indicates that anoxia to striated muscle is a most serious factor in disruption of cell integrity.[52–54]

There are several other diseases, the pathologic mechanisms of which have been investigated more thoroughly, that may be compared

to the myoglobinurias. The defect in the hemoglobin of sickle cell anemia, for example, is the replacement of a single specific amino acid by another that occurs as a genetic recessive trait.[55,56] Certainly, it is not inconceivable that a similar situation might arise in the production of the myoglobin molecule. In fact, several lines of evidence suggest this. The studies of Singer and associates[57,58] have shown that a fetal myoglobin quite different structurally from adult myoglobin exists, a situation analogous to that of hemoglobin. There are abnormal hemoglobins that do not appear until close to adulthood.[59] Again, if this were true of myoglobin, it might explain the onset of the disease during late adolescence in the exertional group. The hereditary factors in the myoglobinurias as previously described seem highly significant. In hereditary spherocytosis, a specific defect in an enzyme related to glycolysis and ATP production seems to be the basis for the inability of the erythrocyte to maintain the structural integrity of its membrane.[60,61] This would be a specific example of increased cellular fragility related to decreased ATP production, as postulated in the pathophysiology of myoglobinuria.

Evidence against this thesis of abnormal myoglobin was presented by Theorell and de Duve,[62] who have compared the myoglobin from the urine of patients with paroxysmal paralytic myoglobinuria and the extracted myoglobin from normal human hearts and found slight differences in light absorption curves, solubility, and crystal formation which were not considered significant; however, the changes of one or more amino acid groups might cause minute and subtle differences such as described. Prankerd[33] electrophoretically compared the myoglobin of normal human muscle with that of the myoglobin found in the urine of a patient with paroxysmal paralytic myoglobinuria and found no significant differences. These studies would not rule out a myoglobin deficiency, which has been found in those cases in which it was tested for. However, further investigation in this direction is indicated. No studies were available on the comparison of equine myoglobin in diseased and normal animals.

In considering where the defect of the myoglobinurias lies, other possibilities such as the cell membrane, glycogen utilization (see addendum), various aspects of the oxidative system in the aerobic and anaerobic cycles, and the myofibrillar structure itself have been considered. Although none of these loci can be ruled out, the preponderance of evidence, as described, implicates a defect in oxygen utilization. There is evidence from other degenerative muscular diseases, such as Zenker's waxy degeneration,[41] that militate against a primary myofibrillar disorder. In this disease, there is wide spread muscle disruption but no myoglobinuria. The cytochrome systems and the anaerobic and aerobic cycles are present throughout muscle tissue. If a primary or secondary defect related to a member of these systems were the cause of myoglobinuria, one would expect cardiac and smooth muscle to be involved also instead of only those muscle groups most dependent on myoglobin. Thus, based on the available evidence, the postulated mechanisms of a qualitative or quantitative defect in the myoglobin and subsequent oxygen utilization seem to be the most likely cause of the exertional and toxic myoglobinurias.

SUMMARY AND CONCLUSIONS

The authors have presented 2 new cases of paroxysmal paralytic myoglobinuria and a critical analysis of the literature. Of the 45 cases reviewed, 40 are subjected to analysis and divided into exertional and nonexertional groups. (Since this writing, 6 additional cases have been noted in the literature.[63–66]) Utilizing this division, other significant differences between the 2 groups are observed. These differences suggest that, in the first group, the disease is precipitated by exertion, usually starts in young adult life, is a chronic problem that lasts many years, and is characterized by a large number of repeated attacks. A family history of myoglobinuria or muscular disease is noted in about one-third of the cases. Complications of weakness and atrophy are not uncommon, and uremia is the most serious complication, although the over-all mortality is not high. Infection is rarely an associated factor. It is suggested that the term paroxysmal paralytic myoglobinuria be reserved for this group.

In the second group, the disease is not precipitated by exertion, although exertion may be

an aggravating factor. The disease is often acute and severe. An infection is present in more than one-half of the cases, and the majority have fever or leukocytosis. The majority of the cases occur during childhood, and most patients have less than 3 attacks. The total duration of the disease is considerably shorter than in the first group, and, while atrophy is a less common complication, uremia is more common and the mortality considerably higher. A positive family history is noted in about one-fifth of these cases. It is suggested that the term toxic myoglobinuria be used to describe cases in this group.

Laboratory, pathologic, and related studies are discussed. The possible relationship to muscular dystrophy is mentioned. Similar diseases in animals and man are also analyzed. The possible pathophysiology of the diseases is discussed, and it is suggested that a relative deficit in oxygen utilization by striated muscle due to a deficiency of myoglobin or an abnormal myoglobin is the major causal factor in the exertional cases. A primary or superimposed toxic factor interfering with the function of the myoglobin is implicated in the nonexertional or "toxic" cases.

ADDENDUM

It has been reported that myoglobinuria may occur in McArdle's disease, in which there is a defect or absence in phosphorylase leading to impaired utilization of glycogen, with consequent decreased ATP production. Pathologically, there is an excess of glycogen in muscle and decreased lactic acid in the serum after exertion. The clinical picture is one of lifelong pain and weakness on exertion, usually involving all skeletal muscles including those of the jaw.[67–69] The symptoms disappear rapidly after rest, and there is no increased tolerance to exertion after rest, as described in the second case reported in this communication. A histopathologically tested muscle biopsy from this patient failed to reveal an excess of glycogen. The clinical picture in the reported cases with myoglobinuria does not suggest McArdle's disease. However, the possibility of this type of defect being a factor in paralytic myoglobinemia of horses and some of the cases presented in Table III must be kept in mind. Certainly, future cases with myoglobinuria should have muscle biopsy tested histochemically for increased glycogen to rule out this disease.

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Problems of anticoagulant therapy in cerebrovascular disease

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For the past twenty-seven months, a study of cerebrovascular diseases has been in progress at Bellevue Hospital. A phase of this study has been concerned with the use of anticoagulant drugs in cerebral thromboembolism.

McDevitt, Groch, and Wright[9] in a preliminary report have briefly discussed this study, including the results of anticoagulant therapy. The present report is concerned with a more detailed analysis of the difficulties and complications which may occur among the population group of a busy city hospital in which admissions are entirely unselected. Materials and methods have been described previously. Patients with cerebrovascular disease admitted to the medical and neurologic wards of the Second Division (Cornell) and to the medical wards of the First Division (Columbia) of Bellevue Hospital constituted the clinical material. The initial evaluation of the patient was carried out by the ward physicians.

Every patient included in the study had a carefully performed lumbar puncture. The patient was then seen by the neurologist of the study group and placed in 1 of 2 categories. Group 1: If the diagnosis of cerebral thrombosis was clearly evident and no known contraindication to the use of anticoagulants existed, a previously randomized selector system was used to determine whether the patient should receive anticoagulant therapy. Group 2: If the evidence supported a diagnosis of cerebral embolism or a stroke accompanied myocardial infarction, the patient received anticoagulants on an obligatory basis and thus was removed from the controlled study. While the patient was still on the hospital ward, daily anticoagulant therapy and routine medical care were directly supervised by the ward physicians, in consultation with the study group. Only when the patient was discharged did the study group assume full control of therapy. Prothrombin times were performed following the Link-Shapiro modification of the Quick test, in which control times are fourteen to sixteen seconds in the undiluted and thirty-eight to forty-two seconds in the diluted plasma (12½% dilution), using lung thromboplastin. The anticoagulants used were provided by the pharmacy of Bellevue Hospital (heparin, Dicumarol, and Coumadin).

DESCRIPTION OF SERIES

Between July 20, 1956, and October 18, 1958, 108 patients with a diagnosis of cerebral thrombosis or cerebral embolism received anticoagulants. Of these, 61 were selected through the randomized system and treated (group 1), and 47 were considered obligatory (group 2). Their ages ranged between 17 and 86 years (Tables 1 and 2). In 54 patients, anticoagulants were discontinued in the hospital; 48 were continued on anticoagulant therapy as outpatients, and 6 were still in the hospital at the time of the report. The majority of the patients were over 50 years of age (Tables 1 and 2).

Table 3 outlines the reasons for not continuing anticoagulant therapy in 54 patients (50%); 14 (26%) were stopped as a direct result of a complication of anticoagulant therapy. The older group of patients in the seventh, eighth, and ninth decades were less likely to be continued on anticoagulant therapy upon discharge from the hospital. Of the initial pa-

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tient group over 60 years of age, 36% had their therapy discontinued while in the hospital. This is 72% of the entire group in whom anticoagulant therapy was discontinued. Table 4 indicates the reasons for discontinuing anticoagulant therapy in outpatients and the point of time at which it was stopped. In the low income group representative of this series, inability to attend clinic forced the dropping of many patients from the outpatient roster.

Over 50% of those in whom anticoagulant therapy was stopped were discontinued by the end of three months. Most difficulty was encountered in maintaining long-term anticoagulant therapy in the elderly patient attending outpatient clinic; 42% of those in whom therapy was discontinued while attending outpatient clinic were 71 years of age or more.

COMPLICATIONS OF ANTICOAGULANTS

Complications occurred in 10 of group 1 (16%) and 12 of group 2 (25%), with a total of 22 or 20% of the series. Of the 22 complications, 14 occurred in the hospital. In the obligatory group, 2 deaths were directly attributed to anticoagulant therapy (2%). No deaths due to anticoagulants have occurred in the treated group selected for the randomized series. These complications will be discussed now in detail.

Deaths

Case 1. M.S., a 66-year-old white man, developed bilateral blindness, lasting twenty minutes, on the day of admission to the hospital. On the same day, he had bioccipital head pain. Four hours after the onset of his symptoms, his vision became blurred and, for a short period, he again was totally blind. On admission, blood pressure was 220/120, becoming 186/95 two days later. The patient was drowsy. There was a left homonymous hemianopsia. Both plantars were extensor. The electrocardiogram revealed nonspecific T-wave changes. The electroencephalogram was diffusely abnormal, right more than left, with delta waves in the right frontal area. Cerebrospinal fluid was clear and colorless, with initial pressure of 180 mm., and contained 1 white blood cell and 50 mg. per cent protein. Diagnosis was basilar artery thrombosis. On the third day after admission, intravenous heparin and oral Dicumarol were started, but the former was discontinued after twenty-four hours. The patient continued to be obtunded, with little change in his neurologic signs. After two weeks of therapy, his blood pressure fell suddenly and could not be maintained on Levophed. Anticoagulants were discontinued on the same day with the prothrombin time at twenty-eight and one-half seconds. However, one week prior to this day, the prothrombin time had been sixty-five seconds, the only time it rose beyond therapeutic range. His condition worsened, and he died forty-eight hours after cessation of anticoagulant therapy.

The autopsy findings were [1] numerous atherosclerotic plaques present in the basilar artery, but

TABLE 1
108 PATIENTS TREATED WITH ANTICOAGULANTS

	Randomized group	*Obligatory group*
Number	61	47
Still in hospital	6	0
Discontinued in hospital or at discharge	23	31
Continued as outpatients	32	16

TABLE 2
AGE DISTRIBUTION OF ALL CASES TREATED

Age	*Randomized group*	*Obligatory group*
11–20	0	1
21–30	0	0
31–40	2	4
41–50	3	6
51–60	16	13
61–70	21	13
71–80	17	10
81–90	2	0

TABLE 3
REASONS FOR NOT CONTINUING PATIENTS ON ANTICOAGULANTS ON OUTPATIENT BASIS

	Randomized group	*Obligatory group*
Number	23	31
Died	6[1]	12[2]
Bleeding complications	4	10[4]
Transferred	9[3]	7
Inability to attend	3	1
Social problem	1	1
Miscellaneous		3[5]

[1]Includes patient discontinued because of necessity for prostatectomy; he subsequently died.

[2]Includes 2 patients transferred to mental institutions

[3]Includes 2 patients whose deaths were considered complications of therapy and 1 death to which anticoagulants probably did not contribute

[4]Includes 3 patients who died

[5]In 2 cases, service chief interdicted therapy on question of diagnosis. In a third, anticoagulants were stopped because of deterioration in patient's clinical state; this was not due to therapy.

TABLE 4

REASONS FOR AND TIME OF DISCONTINUING ANTICOAGULANT THERAPY IN OUTPATIENTS

Reason	Time on anticoagulant therapy as outpatients				
	< 1 month	*1–3 months*	*4–6 months*	*7–12 months*	*>12 months*
Inability to attend clinic	4	2	0	1	2
Poor anticoagulant control	1	0	2	0	0
Complications	1	2	0	1	1
Unrelated illnesses	0	0	1	0	1
Totals	6	4	3	2	4

no demonstrable occlusion; [2] rudimentary posterior communicating arteries without visible lumina; and [3] a recent hemorrhage, 4.5 x 3.3 x 2.2 cm., in the right occipital lobe near the occipital pole. The pathologist estimated that the hemorrhage was three days old.

Comment. It is difficult to see how one could avoid the diagnosis of basilar artery occlusive disease in this patient. However, the hemorrhage probably occurred after treatment with anticoagulants.

Case 2. F.G., a 77-year-old white woman, suddenly became dizzy and lost consciousness during an examination in the gynecology clinic. She was admitted to the Neurology Service on November 8, 1956.

On physical examination, blood pressure was 150/90. She was drowsy and had a severe dysarthria. She had ophthalmoplegia, diminished corneal reflexes bilaterally, absent gag reflex, and an extensor plantar response on the right. Cerebrospinal fluid examination disclosed 300 red blood cells with xanthochromic supernatant fluid and 53 mg. per cent protein. The next day, examination showed 500 red blood cells with xanthochromic supernatant fluid and 85 mg. per cent protein. On November 16, 900 red blood cells with xanthochromia and 45 mg. per cent protein were found. The same day, the patient was found to have an acute left iliofemoral vein thrombophlebitis. Because of a rapidly ascending progression of the thrombophlebitic process, she was given intravenous heparin and oral Dicumarol. She died two days later, November 18. Postmortem examination revealed multiple atheromatous plaques in the blood vessels at the base of the brain. Sections of the brain stem showed 1 recent large hemorrhage, 3 x 4 cm., in the pons.

Comment. Because of the presence of red blood cells and xanthochromia in the spinal fluid, this patient should not have been given anticoagulant therapy, despite the severe venous thrombophlebitis.

Case 3. R.G., a 55-year-old Negro man, was found at his place of work with a right hemiplegia and aphasia on August 26, 1957. Initial examination showed blood pressure to be 150/90. Auricular fibrillation was present. Neurologic examination revealed a complete aphasia and right hemiplegia, right hemihypalgesia, and right extensor plantar response. Lumbar puncture was performed the next day, and a traumatic tap occurred. A repeat cerebrospinal fluid examination one week later showed slight xanthochromia. Ten days after admission, the patient developed clinical findings of multiple pulmonary emboli, and 75 mg. of heparin was given intravenously five hours before death. Autopsy findings revealed multiple hemorrhagic infarcts in the cerebral hemispheres and a recent hemorrhage. There were multiple pulmonary emboli, one of which was massive, for which no source could be discovered.

Comment. Almost certainly, in this patient, emboli to the cerebral vessels had occurred because of the hemorrhagic nature of the infarcts and the presence of pulmonary emboli.[1] Such a case would be considered suitable for anticoagulant therapy. The evidence suggests that it played no part in the cause of death.

Major Complications (6%)

Case 4. F.K., a 45-year-old white man, had a seizure followed by aphasia and right hemiplegia on the day of admission. Blood pressure was 160/100. Cerebrospinal fluid was normal. On April 10, 1957, six days after admission, a left carotid angiogram showed a complete occlusion of the left middle cerebral artery. Oral Dicumarol was started on April 15. On April 19, the patient was somnolent and had a temperature of 103° F. Repeat cerebrospinal fluid examination showed an initial pressure of 260 mm. with marked xanthochromia and a protein of 215 mg. per cent. His prothrombin time had never exceeded therapeutic range. He was treated with 50 mg. of vitamin K_1 intravenously and was much better the next day. He continued to improve, but his hemiparesis persisted. One year later, on follow-up, he was essentially unchanged.

Comment. The evidence for cerebral thrombosis was substantial. The xanthochromia in the second cerebrospinal fluid test indicated

intracranial bleeding. This could have been secondary to a hemorrhagic infarct from an occlusion at a higher level than that shown by the angiogram or to a primary intracerebral hemorrhage. Under such circumstances, it might not have been produced by the anticoagulant therapy.

Case 5. H.T., a 51-year-old Negro man, had a diagnosis of right middle cerebral artery occlusion established on September 12, 1957. Anticoagulant therapy was started September 17. His blood pressure varied between 180 and 220 systolic and 100 and 120 diastolic. Anticoagulant therapy was supervised by residents on the home care program and not by the study group. Between December 17 and December 31, a steady rise was noted in his prothrombin time to forty-one seconds in the undilute. Despite this, anticoagulants were continued. On January 5, he was readmitted to the hospital because of severe abdominal pain. The prothrombin time was sixty seconds. He was given 50 mg. of vitamin K_1 intravenously, and an exploratory laparotomy was performed because of signs of intestinal obstruction. At surgery, 2 ft. of hemorrhagic jejunum were removed. His subsequent progress was satisfactory. Anticoagulant therapy has not been reinstituted.

Comment. This is an unusual complication of anticoagulant therapy but has been described previously.[15] In this instance, it was apparently a direct result of misjudgement of dosage.

Case 6. J.D., a 72-year-old white man, was admitted to the hospital on October 29, 1957, with a right hemiparesis and aphasia. Blood pressure was 140/70. The next day, a left carotid angiogram revealed no abnormality. The cerebrospinal fluid was normal. He was treated with anticoagulants for ten months and did well until August 6, 1958, when he came to the anticoagulant clinic of the outpatient department complaining of severe occipital headache. No new signs were found on physical examination. He was readmitted to the hospital, and the spinal fluid examination revealed fluid at a pressure of 120 mm., 6,000 red blood cells, and xanthochromic supernatant fluid, with a protein of 115 mg. per cent. The prothrombin time was forty seconds (control fourteen seconds), which is at the outer limits of therapeutic range. The patient was treated with 100 mg. vitamin K_1 intravenously and subsequently showed satisfactory progress. A right carotid arteriogram revealed no abnormality. He was discharged feeling well and with little functional disability.

Comment. Despite the fact that the patient's prothrombin time was not excessively prolonged when the subarachnoid bleeding was diagnosed, this complication should be considered to be a probable result of anticoagulant therapy.

Case 7. L.W., a 78-year-old white man, developed a left hemiparesis on July 5, 1957. A diagnosis of cerebral thrombosis was made. Anticoagulant therapy was started on July 9 and was continued for fifteen months, while the patient was seen weekly in the clinic. On October 3, 1958, he stated that he had had melena for six weeks, a fact which he hitherto had not disclosed to the study group. The prothrombin time was found to be seventy-nine seconds in the undilute. He was readmitted to the hospital, where investigation revealed diverticulosis of the left colon, but no definite etiologic link between the bleeding and these pathologic changes could be established.

Comment. Only after hospitalization did we learn that the patient, on his own volition, had taken as much as 4 gm. of aspirin a day for two weeks prior to admission. This may well have resulted in the elevated prothrombin time found at admission. However, during the period of six weeks when he said he was having melena, the prothrombin time varied between nineteen seconds and thirty-eight seconds. This case illustrates that even a weekly clinic visit may be offset by a patient's habits and eccentricities.

Case 8. W.A., a 55-year-old Negro woman, was admitted to the hospital on August 28, 1958, with a left hemiparesis. Anticoagulant therapy was started the next day. On September 24, through an error, she received 10-mg. Coumadin tablets in place of the prescribed 5-mg. tablets and so, for a week, received a double dosage. The patient was readmitted on October 1, with pain in the left lower extremity of two days' duration. She was found to have tenderness in the left buttock and the back of the left thigh and anesthesia to pinprick and light touch over the left foot. Straight leg raising was limited to 10° on the left and was normal on the right. The prothrombin time was seventy-five seconds on admission. She was treated with 75 mg. of vitamin K_1 intravenously. Recovery was almost complete at the time of discharge from the hospital three weeks later.

Comment. This patient probably had bleeding into the sheath of the lumbosacral plexus or sciatic nerve from overdosage of anticoagulants.

Case 9. S.T., a 62-year-old white man, was admitted to the hospital on April 1, 1957, with a left hemiparesis. Electrocardiogram revealed a recent myocardial infarction, and anticoagulant therapy was started. On May 25, melena with a marked drop in blood pressure and hematocrit occurred. Anticoagulant therapy was discontinued, and vitamin K_1 and blood were given. No satis-

TABLE 5

AGE DISTRIBUTION OF PATIENTS WITH COMPLICATIONS

	Age group						
	0–20	*21–30*	*31–40*	*41–50*	*51–60*	*61–70*	*71–80*
Randomized group							
In hospital	0	0	0	1	1	1	1
Outpatients	0	0	0	0	2	1	3
Obligatory group							
In hospital	1	0	0	0	1	4	4
Outpatients	0	0	0	0	0	2	0
Total	1	0	0	1	4	8	8
Total patients in age group	1	0	6	9	29	34	27
Per cent complications per decade				11	14	24	30

factory explanation for the bleeding was found. The prothrombin time on May 24 was twenty-six seconds, and, on May 25, it was twenty-two and one-half seconds. Subsequent investigation of the gastrointestinal tract revealed no source for the bleeding.

Comment. Lacking a pathologic basis for the bleeding, it is felt that anticoagulant therapy probably played a part in it, although it is noted that the prothrombin time was never considerably prolonged. A lesion producing a break in the gastrointestinal mucosa probably was the primary cause of the hemorrhage.

Mild complications due to anticoagulant therapy occurred in 6 patients (6%). None of these was associated with excessive prolongation of the prothrombin time.

In 7 patients (6%), bleeding resulted from unrelated and previously unrecognized pathologic states, such as carcinoma of the colon. Unmasking or revealing of a latent pathologic state by anticoagulant therapy is well recognized and may prove of great value.[18] When bleeding was recognized, in no instance was the prothrombin time prolonged beyond the therapeutic range. This is an unavoidable incident in anticoagulant therapy.

The following patient requires brief mention. A 16-year-old Puerto Rican girl with rheumatic heart disease was admitted to the hospital on March 3, 1958, because of headache and left hemiparesis. The next day, she had a generalized seizure and transient auricular fibrillation was noted. On March 5, a lumbar puncture was performed and was thought to be traumatic. On March 7, she was started on anticoagulant therapy by the medical ward physicians, with a diagnosis of multiple cerebral emboli secondary to rheumatic heart disease. The left hemiparesis improved over the next few days, but, on March 10, she had severe headache, a stiff neck, and bilateral extensor plantar responses. Lumbar puncture now revealed a xanthochromic spinal fluid with a protein of 69 mg. per cent. Anticoagulant therapy was discontinued, and, on March 21, a right carotid arteriogram demonstrated an aneurysm of the right middle cerebral artery, which was subsequently ligated by direct surgical approach. She made an excellent recovery.

Comment. There is reason to believe that the first lumbar puncture was not traumatic but represented spontaneous subarachnoid bleeding and that this patient should not have received anticoagulant therapy.

AGE DISTRIBUTION OF COMPLICATIONS

Table 5 shows that, in really aged patients, there is an increased incidence of bleeding complications. Nevertheless, in the face of strong indications, age itself is not a contraindication for the use of anticoagulants. One of the authors (ISW) has instituted and maintained anticoagulant therapy for more than five years in patients over 80 years of age. In addition, there was no correlation between age and severity of the complications.

PRESENCE OF HYPERTENSION

No clear association is apparent between bleeding complications and the presence of moderate hypertension. However, no patient

in this study with a persistent elevation of diastolic blood pressure above 120 mm. Hg was considered for anticoagulant therapy. In 2 patients with severe bleeding complications, the blood pressure on admission was markedly elevated. However, during hospitalization, the blood pressure levels stablized below 200/120 before anticoagulants were started.

REBOUND PHENOMENA

Recent work by Carter and associates[2] has shown that clotting phenomena have a greater tendency to occur in the period up to six weeks after cessation of anticoagulant therapy. We have seen this phenomenon occur in 2 individuals and possibly a third.

1. H.McP., age 54, had been on anticoagulant therapy for a period of eleven months following an acute myocardial infarction and thrombophlebitis. Because of his failure to attend clinic consistently, anticoagulant therapy was discontinued. Two weeks after this discontinuance, the patient developed a thrombosis in the right internal carotid circulation with resultant moderately severe left hemiparesis. Anticoagulant therapy was then restarted, and no additional occlusive disease has occurred for a period of nine months.

2. L.R., age 68, was placed on anticoagulant therapy following a thrombosis in the left middle cerebral artery. He did well until ten months later, when he was admitted with a high fever and signs of a right lower lobe pneumonia. He had a prothrombin time of greater than three minutes in the undilute, but this was restored to normal with intravenous vitamin K_1. Four days after the prothrombin time had been restored to normal, he developed another intracerebral thrombosis and died two days later.

3. This 62-year-old patient experienced a thrombosis in the side opposite the original lesion sixty-five days after cessation of anticoagulant therapy. Anticoagulant therapy was reinstituted, and he made a satisfactory recovery.

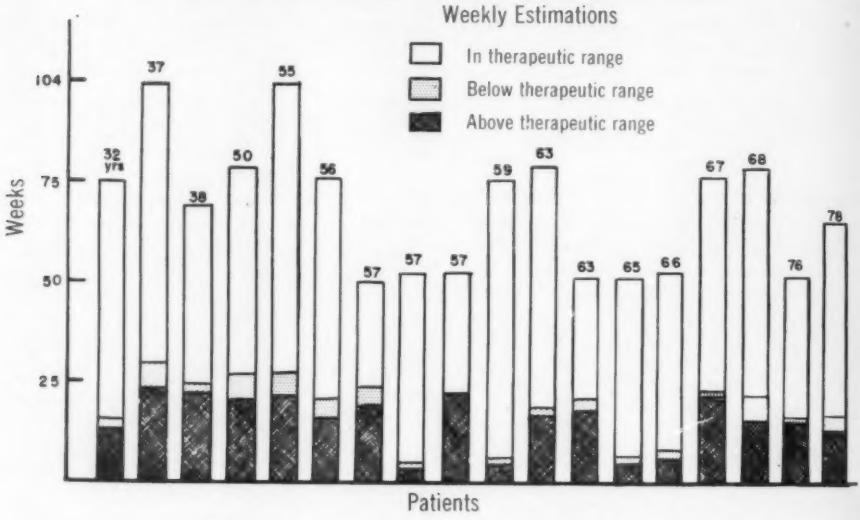
DISCUSSION

Evidence is good that anticoagulant therapy is efficacious in transient ischemic attacks in the basilar[10] and carotid circulation[11] and that, in any type of cerebral thromboembolism, it reduces the number of recurrent episodes.[4,5,7,8,9,12] In addition, review of the results of the first two years of the present study at Bellevue Hospital[9] indicates that the incidence of recurrent thromboembolism was reduced in the randomized treated group as compared to the randomized control group. Also, the fatality rate in the randomized control group was greater than that of the treated patients; 43% of all deaths in the control group but no deaths in the treated groups were due to recurrent thromboembolism. Moreover, no deaths in the randomized group of patients receiving anticoagulants were due to hemorrhagic complications. These results, while at present not statistically significant, are in accord with previously reported experiences.[7,8]

These results were obtained in a setting that is not entirely ideal. The patient group in toto was derived from a low income group that experiences a multiplicity of deficiency states and cannot, for many reasons, maintain the required regular attendance at weekly outpatient clinics. In addition, the present study at times dealt with individuals whose whereabouts became unknown and who therefore were difficult to follow with the required regularity. In the light of these qualifying features, the results to date are far from discouraging.

Against these advantages must be weighed the disadvantages of a treatment which has certain inherent risks. These stem not only from the pharmacologic properties of the drugs but, in such long-term treatment, from the ordinary hazards of living—traumatic accidents such as occurred in one of our patients may lead to situations in which decreased coaguability of the blood is dangerous. As mentioned above, abrupt discontinuance of anticoagulants is risky and may result from the whim of the patient or the unwitting action of a physician during intercurrent illness. There is the ever-present fear of cerebral hemorrhage, which is more peculiar to cerebrovascular disease than bleeding from diseased coronary vessels in myocardial disease. One must weigh, in addition, the known prognosis of a pattern of cerebrovascular disease. Thus, in the lateral medullary syndrome due to thrombosis (Currier and associates[3]) or internal carotid occlusive disease, many years may pass without a further attack. In view of the variability in the natural history of the disease, a large number of randomized patients must be followed for a prolonged period of time before any conclusions can be reached as to the value of the treatment. There are obvious difficulties in maintaining a perfect attendance of such patients in an outpatient clinic because a high proportion of them fall into the older age

TABLE 6
ANTICOAGULANT THERAPY FOR LONGER THAN ONE YEAR.
DEVIATIONS IN PROTHROMBIN TIME FROM THERAPEUTIC RANGE



groups and because of the relative frequency of motor weakness, aphasia, and mental deterioration among these individuals.

In this series, hemorrhagic complications occurred in 22 patients (20%) and included 2 deaths (2%), 6 severe complications (6%), 6 mild (6%), and 7 associated with underlying disease (6%). The complications discussed include some caused by mistakes that are unlikely to be made in the future. The too ready acceptance of a bloody spinal fluid as traumatic or the failure to heed the warning of a xanthochromic spinal fluid should not occur again, but a hard core of bleeding complications must be expected.

Various authors have previously reported the complications from the use of anticoagulants in both myocardial and cerebrovascular disease. McDevitt and associates,[7] in a study of 100 cases of cerebrovascular disease, noted 51 episodes of bleeding in 30 of 100 patients who were being maintained as outpatients on long-term therapy; 5 patients had intracranial cerebral hemorrhage (5%), and 3 died (3%). The other 2, who had subarachnoid bleeding, recovered.

In long-term anticoagulant therapy in patients with myocardial infarction, cerebral hemorrhage has been described as a complication. Nichol and Borg describe 2 cases in 78 patients (3%).[13] Nichol and associates,[14] in a series of 1,091 patients with coronary artery disease, had 6 who died with cerebral hemorrhage (0.5%). These authors also describe 4 individuals with hematoma involving peripheral nerves, such as was seen in 1 patient in this series. Grant and MacMillan,[6] in patients with either coronary or cerebral artery disease, found bleeding complications in 31%, none fatal. Tulloch and Wright[17] described 2 instances of cerebral hemorrhage in 43 patients treated (4%); 1 occurred with a prothrombin time of forty seconds.

In the group of patients we have described, a weekly prothrombin time for the vast majority and biweekly estimations for a very few seemed to be essential to safe and proper management. This presents a difficulty for working people, housewives, and elderly folk. Provisions must be made for vacations, and the outpatient anticoagulant therapy team must be prepared to deal with this and the many other social problems which may arise.

It is necessary to emphasize how often in a long-term program of anticoagulant therapy, with the drugs presently used, prothrombin

times will fall below the minimum therapeutic value of twenty-five seconds or will exceed the forty-second upper limit of the therapeutic range (Table 6). It is impossible to maintain any large group of patients within therapeutic range for a prolonged period of time. This does not detract from the possible value of anticoagulants but points out that presence of continuous protection cannot be assumed.

Finally, we see from this study of 108 patients started on anticoagulants (excluding 6 still hospitalized) that 54 patients of those discharged from the hospital were not continued in outpatient clinics. Of the remaining 48, 19 were discontinued as outpatients. Only 29 of the total 108 patients were receiving anticoagulant therapy as outpatients at the time this report was written. The 108 patients were themselves derived from 362, those rejected being either controls (1/6 of the entire group) or unsuitable for anticoagulants because of definite contraindications or social problems. Approximately 33% of all patients with strokes will be suitable candidates for anticoagulant therapy. Of this number, there may be, in settings similar to the present study, a significant loss of patients because of complications and inability to attend outpatient clinic.

SUMMARY

The problems and complications that arose in the course of anticoagulant therapy in patients with cerebrovascular disease are described in detail. Of 108 patients treated, a total of 22 (20%) had hemorrhagic complications. The incidence of complications was greater (26%) in the group of patients in whom therapy was considered obligatory than in those who were selected as part of the controlled study (16%). A hemorrhagic complication necessitating discontinuance of therapy occurred in only 1 of 18 patients followed for more than twelve months.

It was found that the older the patient, the greater the incidence of complications; yet 8 patients more than 60 years of age were able to attend clinic for longer than twelve months. Thus, while anticoagulant therapy for cerebrovascular disease is certainly feasible, it involves definite risks and problems. Great care and consideration should be exercised before giving anticoagulants to patients with cerebrovascular disease, and vigilance must be maintained throughout the period of actual therapy.

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Tornado epilepsy simulating Ménière's syndrome

Report of 4 cases

J. M. Nielsen, M.D.

THE CONCEPT that episodes of Ménière's syndrome (episodes of vertigo, nausea, and vomiting) can be manifestations of epilepsy is not new, though largely ignored in the last decades. Hartmann and di Gaspero[1] credit Arnold Pick[2] with the first description of the condition as epilepsie rotatoria in 1903. Dejerine[3] gave a good account in his *Semiologie* in 1914, and Bing,[4] in 1932, outlined it clearly. The authors admit that the attacks of vertigo and falling of this syndrome simulate those due to brain stem pathology but state that they are of "cerebral" origin.

The line of demarcation between a typical Ménière attack and a minor epileptic manifestation is by no means sharp. Patients with a tumor of the cerebellopontine angle (and many without one) are often taken with attacks of sudden vertigo with vomiting and falling but recover completely in a few minutes. They commonly admit that they have no recollection of the fall but suddenly find themselves on the ground and are soon able to rise and resume their former activity. Whether they are momentarily unconscious is difficult to ascertain.

Dizziness, but not vertigo, is a frequent accompaniment of a petit mal attack, but, because of the associated disturbance of consciousness, the patients cannot give accurate descriptions. It is with the cases of retained consciousness but clear-cut manifestations of epilepsy that this paper is concerned. The patients used the term *tornado* to describe their attacks; 4 cases are reported, all in women. The sex "susceptibility" is probably a coincidence.

REPORT OF CASES

Case 1. Mrs. Mary M., a married white woman 38 years of age with 2 children, was referred because of "attacks like tornadoes" for sixteen years. The patient was the second of 2 siblings born at home, but details were not available. She had had the milder acute exanthemas but neither scarlet fever nor diphtheria. She had had a tonsillectomy and removal of a mole from behind the right ear, but this was eleven years after her attacks commenced.

The present illness began at age 22 with attacks of twisting of the left arm at night. With the twisting, which consisted of flexion of the forearm across the chest and severe pronation, was a feeling of rotation and roaring off into space, as in a tornado. After the attack, she would have a good night's sleep. She became tolerant of these attacks and gave no serious thought to them until one night, when, after an attack, her mother found it impossible to awaken her and the loss of consciousness aroused concern. Loss of consciousness became a regular occurrence, but she would awaken spontaneously in about half an hour, usually after the doctor had arrived.

She married at age 23 and soon became pregnant; her obstetrician gave her Nembutal and phenobarbital, but these gave no relief. During her second pregnancy, she had a different obstetrician who referred her to a neurology clinic. She was given no information concerning findings, but an electroencephalogram was taken and a diagnosis of nocturnal epilepsy made.

Treatment with Dilantin changed her attacks so that she no longer soared off into space, but the torsion was unaltered. When seen by the author, she was still having 1 bad night about every six weeks and her forearm had become numb. Roentgenographic examination of the neck had shown spina bifida. As provocative factors, she

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Read at the eleventh annual meeting of the American Academy of Neurology, Los Angeles, April 16, 1959.

had noted severe fatigue and car and seasickness; the attacks tended to come a week after menstruation. There was no history of cacosmia.

Physical examination showed a woman of average build with a temperature of 98.8° F. The films showed a moderate spina bifida cervicalis. Blood pressure was 140/82 and the pulse rate, 75 per minute.

A complete neurologic examination, including fundi, fields of vision, pupils, hearing, and all deep and superficial reflexes, was entirely negative. Sensory perception was normal even in the left hand. The strength of her grip was above average for a woman in both hands (readings of 98 and 72, respectively, on the dynamometer).

Comment. The torsion of the left arm was strongly suggestive of an irritative lesion in area 6 on the right, but such a lesion would not explain the roaring sound or the delusion of leaving the planet. An irritative temporal lobe lesion could explain the torsion and the sound. Since the lesion had been present for sixteen years, a surgical lesion was extremely unlikely.

Case 2. Mrs. Dorothy S., a widow aged 42 years, was referred because of attacks of vertigo with vomiting and falling since the age of 12. The patient was the fifth of 6 siblings, born at home in Missouri. During her childhood, she had upper respiratory infections complicated with otitis media and tonsillitis. She also had measles and mumps. Her periods were normal. She had had tonsillectomy and appendectomy and had suffered a great many falls associated with her vertiginous attacks.

At first, the patient insisted that she never lost consciousness in her episodes, many of which were nocturnal. After intensive questioning, she constructed the following history on the basis of many additional important symptoms she had considered irrelevant but which were brought out by specific questioning.

In a typical attack in childhood, she would be seized with a feeling of vertigo and the environment spinning around her like a top, as though she were in the center of a tornado. If she was erect, she would grasp her head, hold it tilted to the right, fall, and have a great deal of vomiting. She habitually suffered with car sickness and could not travel. She would always be dizzy on change of posture. She never had any noises in her ear or head but smelled disagreeable odors about her; her sense of taste was so disturbed that she was unable to eat many types of food because of a bad taste and odor.

If an attack came while she was lying down, she could avoid vomiting; if she could remain immobile, the attack would soon end "and the room would come back into focus." With the attacks, she usually had severe headache "at the base." After an attack, she would still smell the bad odor and have a compulsion to sleep.

As time went on, the attacks changed slightly in that the whole world would spin and in a much greater arc. Otherwise, there had been no change in thirty years.

She had seen very good otologists who found a nerve deafness on the right and told her that a hearing aid would not help. She took Dramamine for a while with a little improvement, but she discontinued it and was taking Compazine.

General physical examination showed a well nourished woman 63½ in. tall and weighing 114 lb. Her temperature was 99.4° F. in the afternoon. Heart tones were clear; blood pressure, 110/80; and pulse rate, 75 per minute. No subjective or objective bruit was heard over the scalp.

Neurologic examination showed hyposmia on the left only. Fundi, fields of vision, extraocular muscles, and pupils were all normal. She was completely deaf in the right ear, but, contrary to expectations, it was conductive deafness, since the Weber test lateralized to the deaf ear. She held her head tilted to the right.

All deep and superficial reflexes were normal, and cerebellar signs were absent. When asked about déjà vu, she admitted that, for many years, she had had the feeling in new situations that "all this was familiar and had happened before."

With the headache, hyposmia, cacosmia, dysgeusia, déjà vu, tendency to sleep after an attack, and history of otitis media with conduction deafness in the right ear, an old right temporal otitic abscess was considered. An air study was advised but refused.

Case 3. A woman of middle age was referred because of tornado attacks. The attacks were all alike and had continued to recur for years. She would be seized by a sudden terrific sense of whirling with roaring in the head and then a feeling of being sucked up into space, as though in a tornado. Then vomiting would begin and continue even after her stomach was empty. There was one factor about these attacks that made them more tolerable—"the most gorgeous heavenly music," the like of which she otherwise never heard. She stated that the ecstasy on hearing the music made the attacks almost worth the trouble. The music would cease with the attack. Past history proved devoid of pertinent information.

A general physical examination showed nothing worthy of note, but a neurologic examination gave increased deep reflexes on the left and a positive Babinski sign. She was referred to Dr. R. B. Raney for study. This disclosed an intraventricular tumor involving the body and inferior horn on the right. The patient died following surgery.

This case is recorded from memory because the records are lost. However, it is important because of verification of the site of the lesion.

Case 4. Mrs. R.L.H., a young woman of 26 years with 4 children living and well, was referred because of attacks of headache, fluttering in the

ears, and severe rotational sensations associated with the feeling of floating out into space, as in a tornado. She had had the usual mild diseases of childhood, tonsillectomy, and appendectomy. She also had been in an automobile accident, but this was after her attacks began and had not altered her seizures. Her menses were normal.

Her essential illness began in January 1958, with a combination of a sensory sensation of fluttering in her ears and a sound like a hummingbird. Since that time (eleven months from the time of giving her history), she has had many episodes which were all essentially alike. There are weeks without episodes.

A typical episode begins with the fluttering and humming, which alone prevents sleep but otherwise is not troublesome; she can even hear over the telephone during it, though sounds are indistinct. Her vision becomes dim, as in a mist. Either before the dimming or during it, her equilibrium is uncertain and she is nauseated. Then the noises change to ringing that holds her entire attention. This is then superseded by a violent spinning sensation and a feeling of being drawn up into space, as in a tornado, and she cannot speak. She can fight these attacks off if she drives herself into some activity, but, for protection, she seeks a chair to sit and await the termination. She does not think she loses consciousness.

However, she has had 2 episodes in which she lost consciousness. During 1 of these, she had a severe headache and suddenly became aware of being across the double line of the road while she was driving her car. In another attack, she found herself far off the road into the desert, where her car struck a bank of earth. She knew she was off the road before the impact but could not regain control in time. Rather than admit loss of consciousness, she claimed she had gone to sleep and was fined for exceeding the speed limit. She liked athletic activities; she was good on water skiis and flew her own airplane without thereby precipitating attacks.

There is also a suggestion of narcolepsy in her case, because she responds to noises with startle and fear; then, if she is standing, her knees give out and she sinks to the ground.

Physical examination showed a well built woman 5 ft., 3 in. tall and weighing 136 lb. Her heart was clear; blood pressure was 130/90 and pulse rate, 90 per minute. Neurologic examination gave only 2 findings, an overfilling of the veins in the fundi and absent plantar responses. The deep reflexes were all small and symmetric.

The diagnosis was epilepsy, and treatment with phenobarbital and Dilantin was recommended. She was also advised not to drive, fly, or water-ski.

COMMENT AND SUMMARY

Reported are 4 unusual patients, all epileptic, all women, and all with severe vertigo and nausea or vomiting, like a Ménière attack, and without loss of consciousness at the time. In 3 cases, the patients had a sensation of whirling off into space, described by them as in a tornado. On the basis of temporal lobe symptoms (déjà vu, cacosmia, dysgeusia) in 1, 2 other episodes of unconsciousness with cacophony in 1, old otitis media in another, and verified intraventricular tumor in the fourth, the tentative localization of the causative lesion in the syndrome is temporal lobe.

Penfield,[5] in human stimulation under local anesthesia, has found parietal stimuli may produce sense of rotation or bodily displacement. Dizziness resulted from similar stimulation of the insular cortex. On the operating table, of course, lower parietal and temporal cortex are hardly distinguishable.

The explanation of the torsion of the left arm in Case 1 is that the secondary motor cortex on the superior bank of the sylvian fissure is irritated and, in turn, projects this irritation to the primary motor cortex.

The alleviation of the attacks by antiepileptic drugs is gratifying, and the negative explorations of the cerebellopontine angles for lesions in a number of instances in my past records is explained.

Such cases raise the question of a possible temporal lobe focus in cases that appear to be clearly Ménière's syndrome with momentary loss of consciousness during the vertigo with falling. A therapeutic trial with phenobarbital and Dilantin would at least seem justifiable in that syndrome.

Electroencephalographic studies were not done because, when patients clearly have epilepsy, we do not need the electroencephalograms to tell us so.

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Neurology

BOOK REVIEWS

Speech and Brain Mechanisms

by Wilder Penfield and Lamar Roberts, 286 pp., Princeton University Press, Princeton, New Jersey, 1959. $6

The material presented in this book formed the matrix for the Vanuxem Lectures given by Dr. Penfield at Princeton University in 1956. Because the audience for these lectures included lay members, medical students, and physicians of all types, the introductory chapters deal with the current concepts of brain anatomy and physiology with particular emphasis upon the interpretive cortex, stimulation of which induces psychical, experiental, and interpretive responses.

The remainder of the book deals with the cortical representation of speech as determined by [1] the Sodium Amytal test, [2] interruption of speech by electrical stimulation of the cerebral cortex, and [3] disturbances produced by cortical excisions. Finally, in the concluding chapter, a strong appeal is made for the teaching of languages early in the educational system when learning is so simple.

Several points in this monograph are noteworthy. The discussion of cerebral dominance and its relationship to language is thoroughly analysed. Although, in the literature, many patients are reported to have had an aphasia in 1 language only, the authors state that such a dissociated aphasia has never occurred in their experience. All languages have been affected to some degree, although 1 may be more disturbed than another. The authors have mapped 3 cortical areas—in the inferior frontal region, the anterior paracentral region, and the posterior Sylvian region—by the method of electrical interference with speech. These 3 areas, the authors believe, are related to the thalamus, especially the pulvinar which has 2-way connections to the posterior Sylvian speech cortex. It is suggested that a lesion of the posterior thalamic region should produce a global aphasia. "Whether stimulation of the posterior end of the thalamus . . . might summon words is not known."

A selected bibliography and short index are appended.

In this monograph, the authors have attempted to explain the disturbances of speech on an anatomic basis without benefit of psychologic concepts. The result is an interesting hypothesis which will require much work to prove or disprove. In so doing, some of the physiologic processes concerned in speech may be elucidated. Neurologists, neurophysiologists, neurosurgeons, and psychologists will want to consult this monograph and will find within its covers much of interest and value concerning the cerebral mechanisms of speech.

A. E. W.

Trigeminal Neuralgia, its History and Treatment

by Byron Stookey and Joseph Ransohoff, 336 pp., Charles C Thomas, Springfield, Ill., 1959. $10.75

A serious attempt to outline the historic background of trigeminal neuralgia and to indicate the current therapy of the condition is made in this volume. The historic section is the most detailed account of this condition now available. A number of interesting points are given which cannot be found in most discussions of this subject. In addition, some unique photographs and articles are reproduced.

The clinical part of the monograph follows an orthodox outline, discussing diagnosis, etiologic factors, and conservative and operative treatment. Interestingly, the authors believe that section of the descending root of the trigeminal nerve has no place in the treatment of unilateral or bilateral tic douloureux. They hold, as well, a dismal view for the success of the so-called decompression of the posterior trigeminal root.

A very extensive bibliography, as well as subject and author indexes, is appended.

This monograph, which incorporates the extensive experience of one of the pioneer neurosurgeons of the New York Neurological Institute is highly recommended to all neurologists and neurosurgeons as an authoritative appraisal of the past and present treatment of trigeminal neuralgia.

A. E. W.

The Clinical Examination of Patients with Organic Cerebral Disease

R. Klein and W. Mayer-Gross, 96 pp. Charles C Thomas, Springfield, Ill., 1957. $3.50

In this book, a separate chapter is devoted to each of the several types of defects of higher level function that may be observed in patients with organic cerebral disease. Major chapters are devoted to aphasia, visual disorders, motor disorders, disturbances of body scheme, and impairment of general psychic functions. Less space is devoted to disorders of time, tactile agnosia, acaculia, and rules of dominance.

Most of the subjects are discussed first from the point of view of data that can be obtained by taking a history and observing the patient. Then, simple methods of direct examination are described. Next follows a discussion of the interpretation of the results and their probable anatomic significance. This general pattern of presentation is followed, where possible, with each of the subjects.

This book is a creditable effort to organize a difficult subject and to give practical guidance in the examination of patients with higher order defects due to brain damage.

J. R. B.

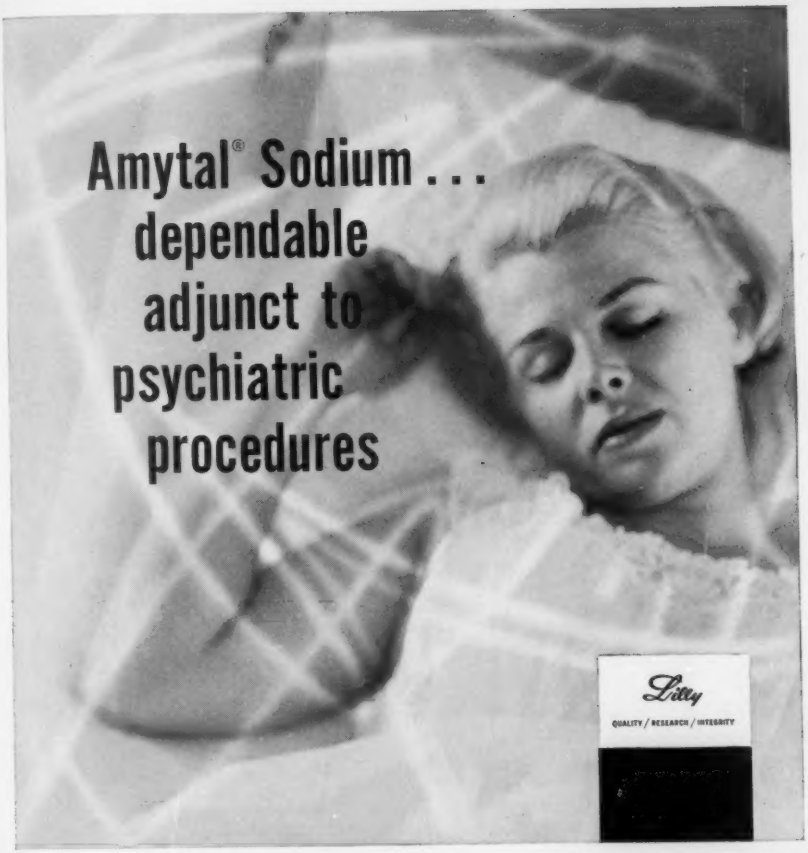
The Treatment and Prevention of Reading Problems

Carl H. Delacato, 122 pp., Charles C Thomas, Springfield, Ill., 1959. $4.50

This book reports uncommon, common, and "universal" traits and factors observed in cases of children who were retarded readers. Low intelligence, emotional conflicts, particular types of schooling, and specific teaching methods seemed to play no important role. Among the "universal" (and presumably significant) characteristics were thumbsucking of the dominant hand, disturbed postures during sleep, evidence of perceptual confusion in spelling or reading, mixed laterality of hand, eye, and foot (lack of unilaterality), and some history of birth complication or long labor. Children with reading retardation seem to possess individual skills but with impairment of ability to organize or integrate these into high-level performances. A "neuropsychologic" approach to treatment and prevention consists first of measures to develop dominance of eye, foot, and sleeping posture homolateral with the preferred hand. Once such an integrated pattern is established, specific reading training may be begun.

The reviewer believes that the thesis proposed has some interesting facets and would seem worth a trial. However, many of the arguments and opinions expressed to support the thesis are neurologically naive.

J. R. B.



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1. Phelps, W. M.: Arch. Pediat. 76:243 (June) 1959. 2. Spears, C. E., and Phelps, W. M.: Arch. Pediat. 76:287 (July) 1959.

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1. Ehrmantraut, W., et al.: Scientific Exhibit Presented at the District of Columbia Medical Society Meeting, Nov. 24, 1958, Washington, D.C.

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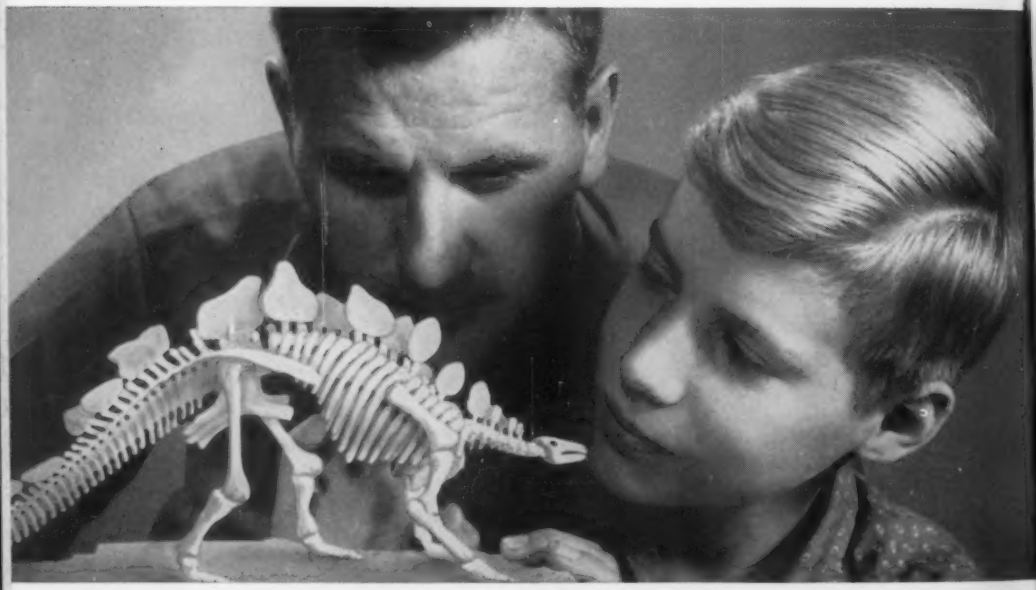

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1. Doshay, L. J.: M. Clin. North America 40:1401 (Sept.) 1956.
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3. De Jong, R. N.: J. Michigan M. Soc. 57:722 (May) 1958.

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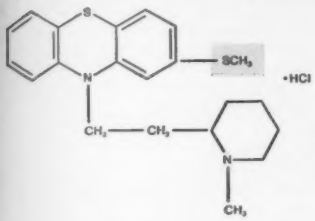

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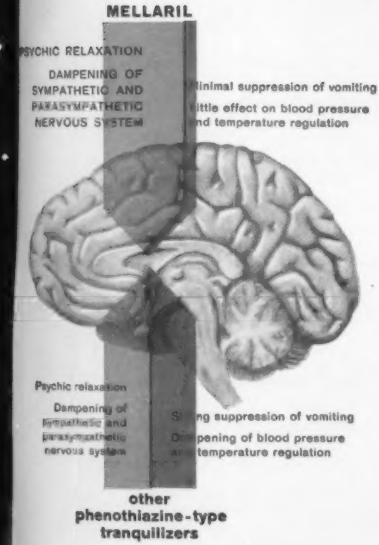
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*Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959

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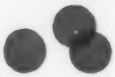

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Krantz, J. C., Jr.: The restless patient—A psychologic and pharmacologic viewpoint. Current M. Digest 25:68, Feb. 1958.

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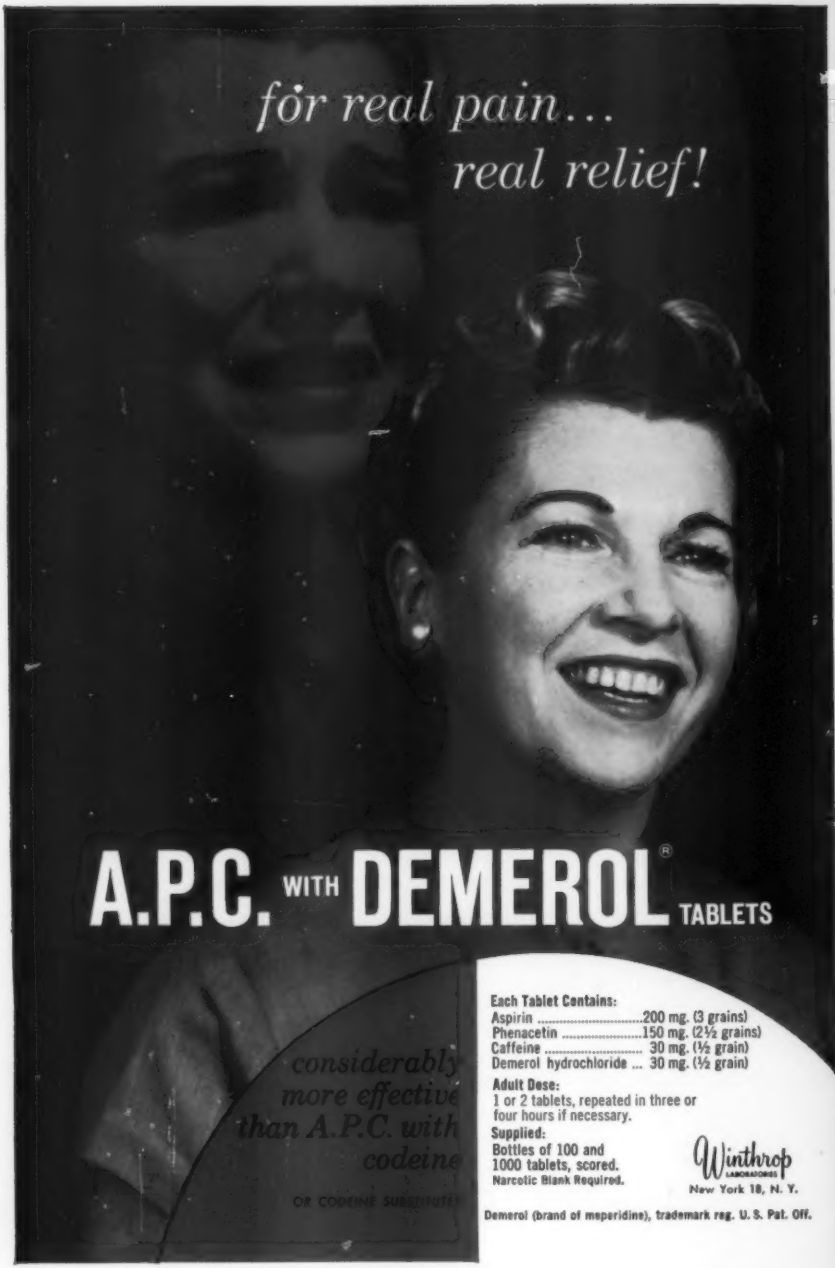
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